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ACTA ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

- The extraordinary case of Henri de Toulouse-Lautrec. Dwarfism in combination with bone fragility
- Can acetabular fractures be successfully treated outside the trauma centre?
- The effect of a pharmaceutical per os supplement based on methylsulfonylmethane, hydrolyzed collagen, bromelain, D-glucosamine, chondroitin sulfate, L-arginine, L-lysine, plant extracts of boswellia, myrr and turmeric, and Vitamin C on Achilles tendinopathy
- The role of jak1/2 kinases in the development of neurogenic heterotopic ossification following spinal cord injury
- The use of botulinum toxin in the treatment of neurogenic bladder following spinal cord injury
- Necrotising fasciitis of the lower extremity following streptococcal pharyngitis
- Young Scientists' Pages (180-209)

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The extraordinary case of Henri de Toulouse-Lautrec. Dwarfism in combination with bone fragility

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ABSTRACT

Henri de Toulouse-Lautrec, a descendant of an aristocratic family from France, lived many years before the application of the achievements of genetics. Suffering from an illness unknown at the time, he was forced from an early age to isolate him self and unfold his unparalleled talent freely, without restrictions. His association with people living on the margins of society, along with his choice to immortalize everyday scenes from their lives on the canvas, compose the enigmatic puzzle of his character. At the same time, his habits, sexual preferences, alcohol addiction, and his premature death from syphilis are the reasons to start an in-depth investigation. The purpose of this study is to elucidate the deeper causes that guided the outlets of his art, at the same time that his short stature, combined with the fragility of his bones, trigger a variety of hypotheses surrounding an underlying inherited disease. Osteogenesis imperfecta justifies certain symptoms. Osteopetrosis involves clinical signs that were absent in Lautrec's case. Pycnodysostosis, however, seems to fulfill the requirements to be unequivocally accused. Our main pursuit, however, is not so much the revelation of the disease from which the artist suffered, as the understanding of his art and the delight given by the correct reading of his works.

KEYWORDS: Toulouse-Lautrec; dwarfism; bone fragility; osteogenesis imperfecta; osteopetrosis; pycnodysostosis

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Introduction

Inherited diseases follow a specific algorithm. After the first observations of Gregor Johann Mendel [1] and the long-term studies that followed [2-4], genetics was able to decipher the laws governing the inheritance of somatic characteristics from generation to generation. The research findings have come so far that we can now hope for a brighter future. The mapping of the genetic material that each cell carries in its nucleus nowadays offers incredible possibilities to researchers for the prevention or effective treatment of an inherited disease [5-7]. The prejudices and stereotypes that pushed our fellow human beings with a deformed and short stature violently on the sidelines are now outdated.

Childhood and Adolescence

Henri Marie Raymond de Toulouse-Lautrec-Monfa was born on November 24, 1864 in Albi, Midi-Pyrénées, South France [8]. His parents were first cousins, a fact that is justified in aristocratic families even today. The financial comfort of the paternal family gave little Henri the opportunity to live happily and carefree his first childhood years. However, after the divorce of his parents, when he was 8 years old, he moved to Paris to live next to his mother. It was the moment when his early talent in painting and sketching became apparent. René Princeteau, a friend of his father, gave the first lessons to the charismatic Henri.

In 1875, at the age of 11, Henri moved back to Albi's hometown because his mother had a health problem and had to visit the Amélie-les-Bains hot springs. His relationship with her was harmonious. He loved and admired her. He considered her a "personalized virtue" and often called her "Juno Lucina". During this period, his mother took the opportunity to seek medical advice for his short stature and developmental delay (Figure 1). Her effort proved futile. At the same time, his father remained inactive, feeding only feelings of shame for his son's strange body type.

At the age of 13, Lautrec had the unpleasant experience of a fracture in his right femur. The following year, he suffered a fracture in his left thigh. These fractures have never been adequately healed. Many researchers attributed the imbalance of his appearance (normal adult trunk and childish short limbs) to this complication [9].

The adolescent years of the small Henri are characterized by isolation and lack of sociability (Figure 2). He did not participate in games with other kids of his age, because he was afraid of causing a new fracture. He was looking for ways to escape reality, in front of the easel, with the paintbrush in his hand. He had to adopt adult behaviors from an early age, depriving himself of the carelessness and innocence that characterize a normal child.

Creative Sensibilities

Lautrec's talent manifested itself early on. His career, however, was favourably influenced by certain coincidences. His advancement in sketching and painting prompted Princeteau to persuade his parents to let him return to Paris. With his own recommendations, he could study next to the famous for his portraits, Léon Bonnat. Under pressure from the Princeteau, the 18-year-old Lautrec officially began his career in Paris in 1882.

The next stages of his creative path developed into a deterministic sequence, as his undisputed talent, and the influence that his aristocratic ancestry could exert at any time, led his steps to Montmartre. The hangout of bohemian life, the meeting point of all kinds of artists, philosophers and writers, was the only place that would be able to accommodate the dreams of the restless student. In Montmartre Lautrec discovered himself. There he showed his creative talent [10].

In the meantime, he moved to Fernand Cormon's studio, where he studied for the next five years. There he met people who would embrace him with their friendship and painters who would influence his style, such as Émile Bernard and Vincent van Gogh. He began to wander the streets looking for topics that would provide solutions to his creative sensibilities. It was then that he met the prostitute Marie-Charlet who agreed to paint her portrait.

In 1885, he took a step forward: he began exhibiting his work at Mirliton, a cabaret that was run

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Figure 1. *Lautrec's father felt ashamed of his son's strange body type.*

Figure 2. *He did not participate in games with other kids of his age, because he was afraid of causing fractures.*

by Aristide Bruant. Two years later, he dared to exhibit his works in Toulouse under the pseudonym Tréclau (anagram of the surname Lautrec). His acquaintance with Suzanne Valadon played a decisive role in his life. He satisfied her coquetry by creating numerous portraits of her (Figure 3). Their relationship never went on until marriage. Valadon attempted suicide in 1888.

After 1888, his career took off. The encouraging reviews for him, the successful exhibition in Brussels, the purchase of his painting by Theo (Vincent van Gogh's brother) for 150 French francs, along with the rise in his self-confidence, played a decisive role. However, what determined his artistic career was his association with prostitutes and his frequent visits to whorehouses. The girls on the margins seemed to have a special charm for this pariah of the establishment who had renounced his arrogant origins; a waste of the aristocracy who was looking for ways to confirm himself. His association with girls stimulated his creative oestrus and gave new impetus to his art. There are about 150 Lautrec paintings and sketches inspired by the prostitutes who accompanied him (Figure 4).

Dwarfism in combination with bone fragility

Science, trying to elucidate the underlying disease from which Lautrec suffered, to clarify why his bones were constantly breaking and his height remained low, relied on biographical data and surviving photographs. It is not an easy task! The knowledge of experts, the perceptiveness of the researcher and the constant scrutiny of the literature need to be mobilized.

Osteogenesis imperfecta is the most common genetic cause of skeletal fragility in a child. It is due to a disease of the connective tissue [11]. The range in which it moves is wide, ranging from the lethal form in the perinatal period to the mild form, the diagnosis of which is often a matter of disagreement. One

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Figure 3. *His acquaintance with Suzanne Valadon, of whom he painted numerous portraits, played a decisive role in Lautrec's life.*

Figure 4. *His association with the girls of the cabaret sparked his creative oestrus and gave new impetus to his art.*

could classify the case of Lautrec in this latter form. However, unspoken doubts and unanswered questions would remain forever, as the data we have on Lautrec's somatic deficit are incomplete.

The disease is characterized by the trinity: fragile bones, blue sclerae of the eyes and early deafness. Limb deformities and short stature can be attributed to multiple bone fractures and their healing in a defective position [12-18]. Considering that, Lautrec did not have a blue colour in the sclerae of his eyes, nor did he have a deformity in the spine, the possibility that he had inherited the disease is considered zero. At the same time, we know that osteogenesis imperfecta is inherited by a dominant (and not recessive) gene. Therefore, at least one of his parents had to suffer from the disease, which certainly did not happen.

Osteopetrosis occurs in two main forms: the severe form, which is inherited by a recessive gene, and the mild form, which is inherited by a dominant gene. For the severe form, we know that it manifests itself from infancy with macrocephaly, hepatosplenomegaly, deafness, blindness and severe anaemia. Pathological fractures are due to the compact configuration of the bone architecture, which makes the lives of patients impossible. Children suffering from this form rarely survive beyond the 2nd decade. In contrast, the predominant form is milder and usually occurs during childhood or adolescence, with fractures and mild anaemia [19-21]. It is clear that

Figure 5. *Pycnodysostosis is very close to successfully describing Lautrec's clinical manifestations* ***a.*** *His height did not exceed 150 cm* ***b.*** *Self-portrait with obvious characteristics of pycnodysostosis.*

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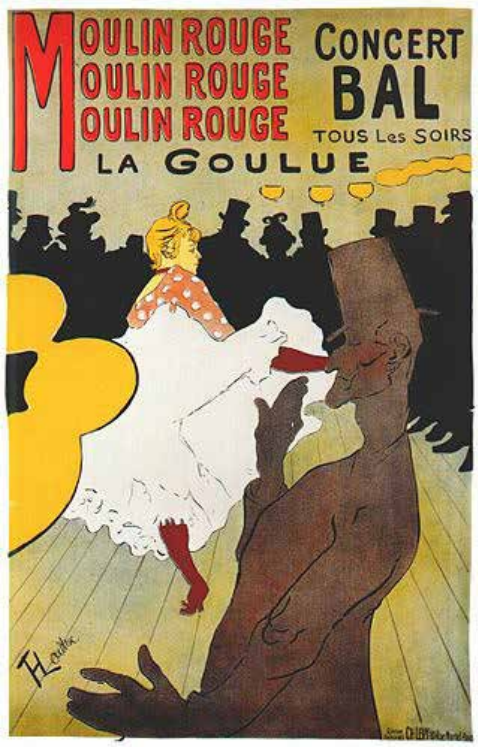

Figure 6. *When the Moulin Rouge cabaret opened, Lautrec agreed to create a series of posters.*

the case of Henri de Toulouse-Lautrec does not agree with either the severe recessive form or the milder dominant form.

Nowadays, the expert opinions converge on pycnodysostosis, as the most likely diagnosis that approaches to successfully describe the clinical manifestations of Lautrec. It is a bone dysplasia inherited with a pathological recessive gene [19, 22]. Appears in early childhood with short limbs, characteristic face, and open anterior fontanelle, large skull, with protrusion of the frontal and occipital bone and abnormalities in dentition. The arms and legs are short and wide. The nails are hypoplastic. The sclerae of the eyes are sometimes blue. Minor injuries usually cause fractures. Patients do not exceed a height of 130-150 cm (Figure 5). In the international literature, one can now find pycnodysostosis with the alternative name Toulouse-Lautrec Syndrome.

Evaluation of the man and review of his work

Lautrec's choice to use vivid colours, the preference to depict scenes of everyday life indoors or outdoors, as well as the emphasis on representing light with personal touches to capture the immediate impression, are characterizing his works. Unsuspecting, he followed in the footsteps of impressionism pioneers such as Édouard Manet και Edgar Degas. He himself hated models. He disparagingly called them "stuffed dolls". He once confessed: "I have found girls of my own size. Nowhere else have I felt so good as if I were at home" [8-10].

Figure 7. *His walking stick was hollow to hide the alcohol there.*

When the Moulin Rouge cabaret opened in 1889, he agreed to make a series of posters (Figure 6). Some of his colleagues rushed to ridicule him, but he remained completely indifferent. The cabaret had a seat especially for him, while he used to display his works. These posters by Lautrec make up a significant part of his work. His unstable soul forced him to turn to alcohol. He started with large quantities of wine and beer but soon resorted to absinthe, which led him to hallucinations. It is said that the walking stick he was holding was hollow to hide the alcohol there (Figure 7). It was not long before he became infected with syphilis.

In February 1899, he collapsed due to chronic alcoholism and the complications of syphilis. It soon became apparent that his mental and physical health would not regain their lustre. He died on September 9, 1901, at the age of 36. After his death, his mother took care to save and promote his work. A museum has been set up in Albi, his birthplace, where most of his works are housed. This is an admirable creation: 737-canvased paintings, 275 watercolors,

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363 prints and posters, 5.084 drawings. However, we know that there are other works (stained-glass works and ceramics) that have been lost [23].

Conclusion

The peculiarity of Toulouse-Lautrec's case lies in the fact that he was able to transform his physical problem into an artistic creation. For us, his strange case simply mobilized and activated our thinking.

Conflict of interest

The authors declared no conflicts of interest.

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ORIGINAL

Can acetabular fractures be successfully treated outside the trauma centre?

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ABSTRACT

Purpose. Acetabular fractures are severe injuries with an uncertain final functional outcome. Methods. We retrospectively analysed 63 patients from 2008. to 2018. We followed complications of surgical treatment for acetabular fractures in 52(82.53%) men and 11(17.46%) women, average age of 45.06 years- old (from 14 to 77). Results. Road traffic accidents were the cause of fractures in 51(80.95%) patients. According to Letournel and Judet 37(58.73%) patients had elementary acetabular fractures, whereas 26 (41.26%) patients had complex fractures. The average follow- up time was 6.15 years (from 2 to 10). Traumatic sciatic/ peroneal nerve injury was present in 9 (14.28%) patients and iatrogenic in 2(3.17%) patients. Early revision osteosynthesis was done in 1 (1.58%) patient, 3 (4.76%) infections and 3(4.76%) patients with deep venous thrombosis (DVT) were present. Heterotopic ossification (HO) was present in 11(17.46%) patients, AVN of the femoral head was diagnosed in 9 (14.28%). Average time of definitive acetabular osteosynthesis was 5.09 days from the injury (from 1 to 21 days). Anatomical reduction of fracture was achieved in 54 (85.71%) patients. Post- traumatic OA was present in 14 (22.22 %) patients. Final functional outcomes, according to Merle d'Aubigné score were: excellent in 20 (31.74%), good in 28 (44.44%), moderate in 11 (17.46%), poor in 4(6.34%) patients. Due to post- traumatic OA and AVN of the femoral head 23 (36.5%) patients underwent THA. Patients underwent THA after the average of 4.28 years (from 1 to 8) after previous acetabular fracture osteosynthesis. Conclusion Complications and results suggest that in addition to the urgent hip reduction in dislocated fractures, early definitive acetabular osteosynthesis and anatomical reduction, the severity of initial trauma significantly have an effect on results. Given the specifics, acetabular fractures require surgical experience and treatment in tertiary care facilities.

KEYWORDS: Acetabulum, Fractures, Treatmnent, Trauma Center

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Introduction

Acetabular fractures have always been drawing orthopaedic's attention and their treatment has always been a real challenge with often an ucertain course of the treatment and the final outcome. The revolution of acetabular fractures treatment started in 1950s by Letournel and Judet [1]. Their acetabular fracture classification is widely accepted and is still used today worldwide [2,3]. The treatment principles which were founded by them are still valid today and those are early open acetabular reduction of fracture and stable internal fixation, early activation [4]. This method of treatment gives good results, but despite adequate surgical work by an experienced surgical team, these fractures are followed by numerous complications such as, traumatic and iatrogenic injury of sciatic/ peroneal nerve, infection, deep venous thrombosis (DVT), heterotopic ossifications (HO), avascular necrosis of femoral head (AVN), post- traumatic arthritis of the hip (OA)[5,6]. Complications such as AVN and OA may require further THA [7,8]. Surgery of acetabular fractures requires extensive experience, which is achieved through special training in national referral institutions or in specialized foreign trauma centres where acetabular fractures are frequent, under the supervision of experienced surgeons. Upon completion of education, in order to maintain a "surgical routine", the surgeon must have a certain number of surgeries in order for the treatment results to be satisfactory. The aim of the study is to analyze the results of surgical treatment of acetabulum fractures and to compare them with the average literature results in trauma centers and to determine whether such operations, which have a low incidence and require additional education and surgical experience, are performed in institutions that are tertiary centers.

Subjects and Methods

Data of patients with an acetabular fracture who were surgically treated in University hospital Nis, Republic of Serbia, a tertiary institution from 2008 to 2018 were analyzed. The study is retrospective, acetabular fractures are classified according to Letournel and Judet [1] classification, early and late complications have been followed as well (Table 1). From surgical approaches, Kocher- Langenbeck approach, anterior Ilio - inguinal, combined, anterior Iliofemoral, lateral- Watson-Jones for total hip arthroplasty (THA) were used. Final functional outcomes of acetabular fractures were determined according to modified Merle d'Aubigné score [9]. Cause of trauma, sex distribution, frequency of nerve injury, infections, DVT, heterotopic ossification (HO), AVN of the femoral head, degree of postoperative reduction were analyzed. Average time of follow-up was 6.15 years (range from 2 to 10 years).

Results

Retrospectively, 63 patients with dislocated acetabular fracture, who required surgery were analysed, 52(82.53%) men and 11(17.46%) women, average age of 45,06 years (range from 14 to 77 years). Road traffic injury was the cause of fractures in 51(80.95%) patients. According to Letournel and Judet 37(58.73%) patients had an elementary acetabular fracture whereas 26 (41.26%) patients had complex acetabular fracture. All of the acetabular fractures were fixated with pelvic and acetabular reconstructive plates. The traumatic sciatic nerve injury was present in 2(3.17%) patients, whereas traumatic peroneal nerve injury was present in 7(11.11%) patients. In total, traumatic nerve injury was present in 9 (14.28%) patients (Fig.1). All of the patients with traumatic sciatic nerve injury or its peroneal division had an acetabular fracture associated with posterior hip dislocation. Iatrogenic peroneal nerve injury was present in 2(3.17%) patients (Fig.2). In 1 (1.58%) patient, early revision surgery of osteosynthesis was done. In this series 3 (4.76%) infections were present after acetabular osteosynthesis, 2 deep and 1 superficial. In 3 (4.76%) patients deep venous thrombosis (DVT) was present. Heterotopic ossification (HO) was present in 11(17.46%) patients, all Broker I, II. AVN of the femoral head was present in 9 (14.28%) patients, in 1(1.58%) patient who had a transverse acetabular fracture and in 8 (12.69%) patients with posterior fracture- dislocation. In 3 (4,76%) patients with AVN of the femoral head, hip reduction was done in the time interval up to 24h from the injury, whereas in 5 (7.93%) patients with AVN, hip reduction was done in the time in-

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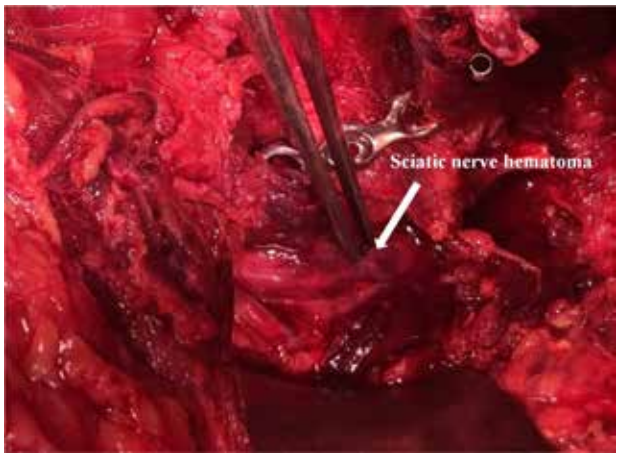

Figure 1. *Intraoperative view after traumatic injury of the sciatic nerve shows sciatic nerve*

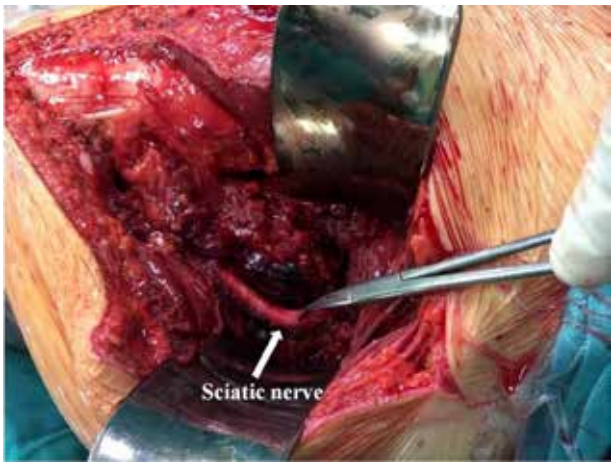

Figure 2. *During the surgical procedure, sciatic nerve needs to be clearly identified and protected.*

TABLE 1.

The rates of complication after acetabular surgery treatment

Traumatic nerve injury	Iatrogenic nerve injury	Infection	DVT	HO	AVN	OA	Revision surgery	THA
9(14.28 %)	2(3.17%)	3(4.76%)	3(4.76%)	11(17.46%)	9(14.28%)	14(22.22 %)	1(1.58%)	23(36.5 %)

terval after 24h from the injury. The average time interval from the injury to definitive osteosynthesis of acetabulum was 5.09 days (range from 1 to 22 days). Anatomical reduction of acetabular fracture, ≤ 2mm, was achieved in 54 (85.71%) patients (Fig. 3,4). Post- traumatic arthritis (OA) was present in 14 (22.22 %) patients. Final functional outcome, according to Merle d'Aubigné score were excellent 20(31.74%), good, 28(44.44%), moderate 11(17.46%), and poor 4(6.34%) (Fig.6). Average time of follow-up was 6.15 years (range from 2 to 10 years). Due to post- traumatic OA or avascular necrosis of femoral head (AVN), 23 (36.5 %) patients required further total hip arthroplasty (THA) (Fig.7,8).

Discussion

Acetabular fractures are followed by numerous complications, which says enough about their specificity and severity [5]. It is thought that Letournel and Judet set the foundation for surgical treatment of acetabular fractures in the 1950s. Their principles are still valid today and their classification into elementary and complex is widely accepted and used [1-4]. Acetabular fractures represent a real challenge for surgeon and their treatment is accompanied by uncertainty, regarding complications and final functional outcome. It is well- known that acetabular fractures are caused by high- energy trauma, by action of the axial force over femoral diaphysis, which can cause different types of fractures depending on the intensity and position of the femoral head in the acetabulum in the moment of impact. The second way in which acetabular fractures can occur is by action of lateral force over the greater trochanter. Acetabular fractures mostly occur in road traffic accidents, according to our results 80.5% of them, and are much more frequent in the male working age population. Scheinfeld et al., Jindal et al., Dakin et al., and Sahu, reported similar results [10]. Our small sample supports the above results. Literature and clinical practice clearly indicate to traumatic injuries of sciatic nerve, most commonly in the peroneal division as a result of dislocated acetabular

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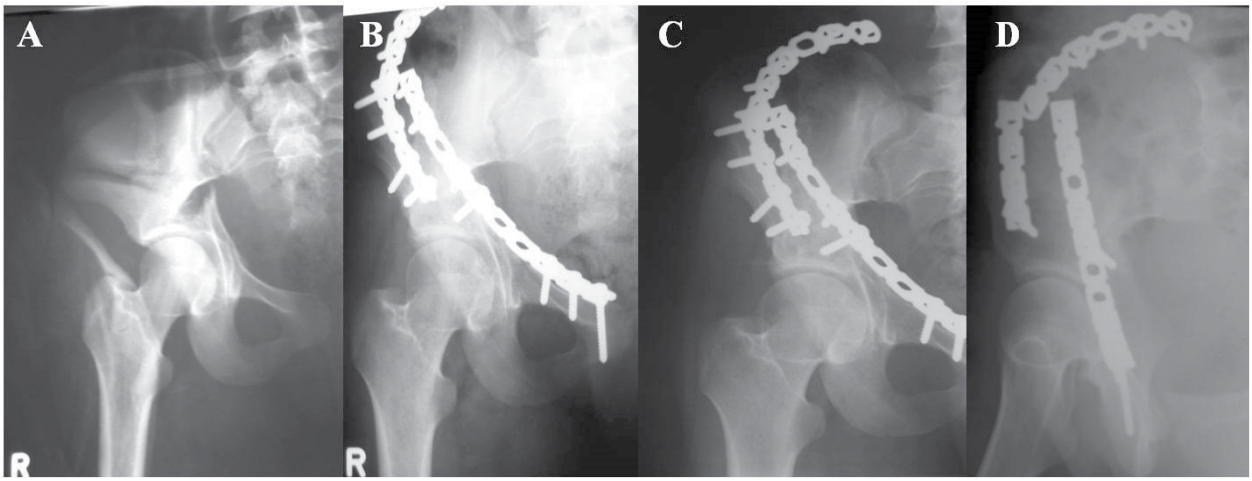

Figure 3. (A-D) *Transverse acetabular fracture associated with iliac wing fracture. A- Preoperative X- ray; B-D- Postoperative X- rays.*

fractures [11]. The cumulative average incidence of sciatic nerve injury reported in the literature is 10% [12]. We had 9 (14.28%) patients with traumatic sciatic and peroneal nerve injury, which was clinically diagnosed immediately after admission. In 3 (33.33%) patients complete nerve recovery was achieved, in 4 (44.44%) partial recovery, whereas in 2 (22.22%) patients there was no neurological recovery. We had 2 (3.17%) iatrogenic peroneal nerve injuries, in both cases complete recovery was achieved. Iatrogenic sciatic/ peroneal nerve injuries are described in literature and can be avoided with careful surgery, nerve identification during surgery and its protection, careful handling of elevators and retractors, setting the knee in flexion during reduction and fracture fixation, hemostasis and postoperative drainage. Giannoudis' meta-analysis of 2426 fractures had an incidence of approximately 4.7% iatrogenic sciatic nerve palsy [13]. Haidukewych et al. published 7.9% traumatic and 5.6% iatrogenic sciatic/ peroneal nerve injuries in a series of 252 patients [14]. Lehmann et al. published that acetabular fractures with the involvement of posterior wall were most commonly accompanied by nerve injuries [15]. According to Simske et al. traumatic sciatic/peroneal nerve injuries occur after posterior fracture-dislocation, transverse fractures, and posterior wall fractures. Peroneal division is usually affected 65%, 50% of patients have partially recovered, 22% of patients had a complete recovery, whereas in 24% of patients with sciatic or peroneal injuries had no recovery. According to the same authors 25% of injuries are iatrogenic [11]. Occurrence of traumatic sciatic nerve injuries cannot be affected on, but urgent reduction of dislocated hip is of utmost importance in order to reduce the femoral head pressure or dislocated bone fragment pressure on the nerve, which latter has a better chance for recovery. Also, early definitive osteosynthesis of acetabulum may play an important role in neurological recovery. Early revision hip surgery is mainly related to debridement and irrigation in infections after osteosynthesis of the acetabulum and reosteosynthesis in loss of fixation [16]. We had 1(1.58%) revision of osteosynthesis and 3(4.76%) patients with infection- 2 deep and 1 superficial. Duration of surgery, obesity, long- term wound exposure, intraoperative hemorrhage are factors which increase the chance of infection. Similar results were published in literature [17,18]. DVT, PTE are described and they accompany this type of surgery, despite prophylaxis. Early definitive osteosynthesis of acetabulum, early mobilization and thromboprophylaxis are important factors for reducing DVT in acetabular surgery [19]. We had 3 (4.76%) cases of deep venous thrombosis (DVT). Wang et al. published that DVT after pelvic and acetabular fracture amounts 29.09% in a series of 110 patients, 48 pelvic fractures and 62 acetabular fractures. Ages 60 and up, associated injuries, complex fractures and postponed osteosynthesis of acetabu-

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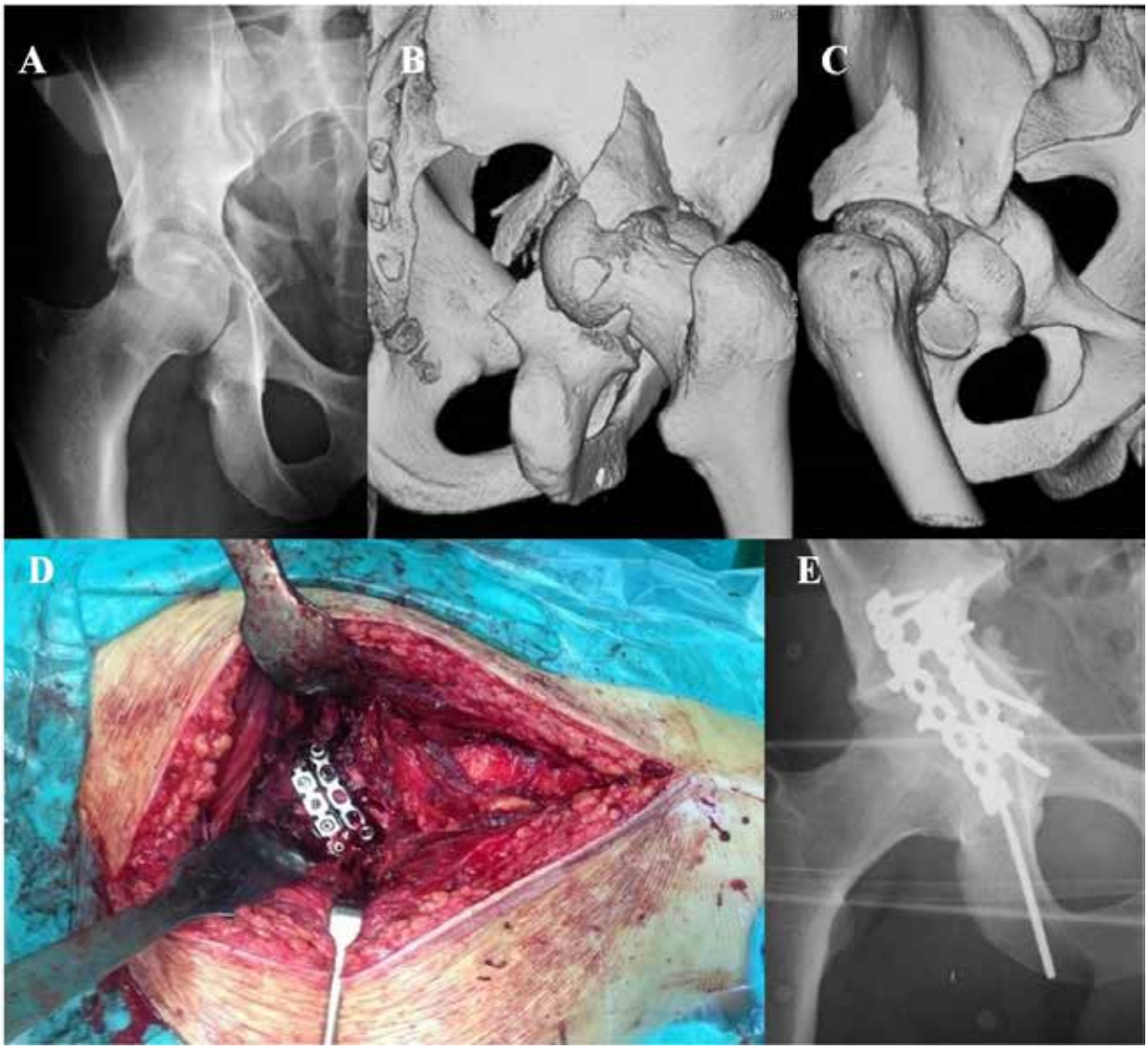

Figure 4. *Transverse acetabular fractures associated with posterior wall fracture- dislocation of the acetabulum. A- X- ray after the injury; B,C- 3D- CT; D- Intraoperative appearance ; E- X-ray after the open reduction and internal fixation.*

lum after 14 days, increase the risk of DVT occurrence [20]. Heterotopic ossification (HO) is also clearly described and it accompanies this type of surgery. In many centres, indomethacin or low- dose radiotherapy is administered as prophylaxis to prevent the development of HO. We did not apply HO prevention in our clinical material. The incidence of 17.46% HO is in correlation with results from the literature [21. The importance of the urgent reduction of the hip is reflected in prevention of AVN of the femoral head. In our series of 63 patients, we had 14.28% cases with AVN of the femoral head, in 1(1.58%) patient who had a transverse acetabular fracture and in 8 (12.69%) patients with posterior fracture- dislocation (transverse/posterior wall, posterior wall, posterior column/posterior wall). In 3 (4.76%) patients with AVN of the femoral head hip reduction were done in the time interval up to 24h from the injury, whereas in 5 (7.93%) patients hip reduction was done in the time interval of 24h after the injury. There are numerous data in the litera-

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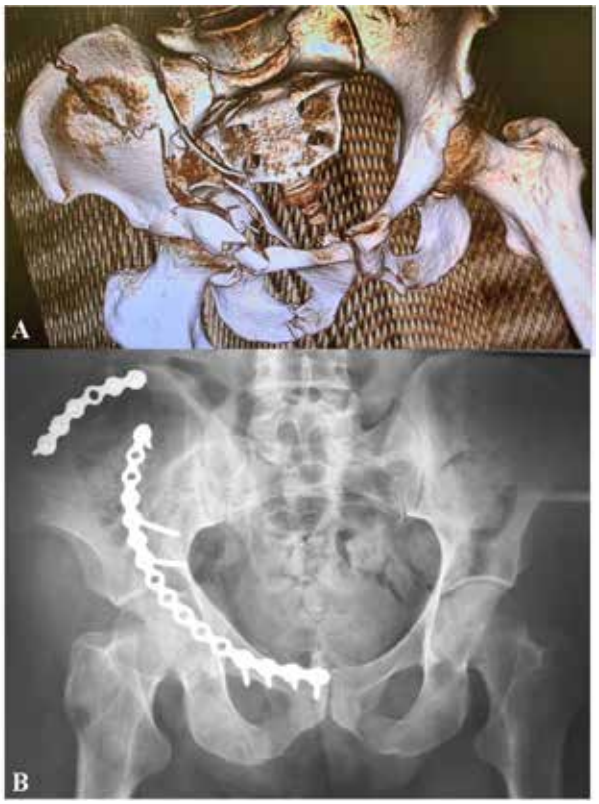

Figure 5 (A,B). *Complex acetabular fracture. A- 3D CT after the injury; B- X- ray after the surgery.*

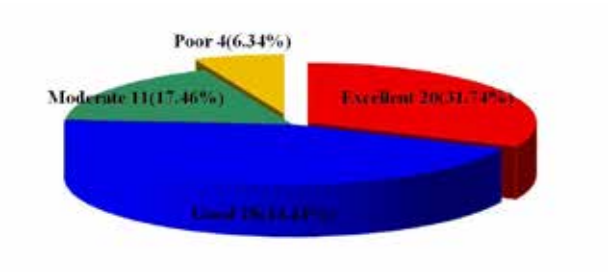

Figure 6. *The end functional outcomes according to the Merle d'Aubigné score.*

ture concerning the importance of urgent hip reduction in acetabular fractures associated with hip dislocation in preventing the occurrence of AVN of the femoral head [22]. In dislocated acetabular fractures, femoral head chondral injury is possible, abrasions, lacerations in the moment of impact. Initial femoral head injury can later significantly increase the chance of AVN of the femoral head occurrence, despite the urgent reduction of the hip. In a small number of cases, orthopaedic reduction of the dislocated hip is not possible due to bone or soft tissue interposition, loose bodies in the hip joint, which is why urgent open reduction of hip and simultaneous osteosynthesis of acetabular fracture are recommended. Upon head impact into the acetabulum, and considering the position of the head during the impact, different types of fractures can occur - elementary or complex. When an acetabular fracture occurs, smaller or larger degree of comminution, impaction, damage of the weight- bearing area of acetabulum, loose bodies in the hip joint are possible. Degree of acetabular dislocation which occurs upon fracture is different, smaller or larger than 20mm. All of these factors have a negative effect on the final outcome, on which we do not have an influence and they indicate that initial trauma can determine final functional outcome [23,24]. Early surgery, right surgical approach, anatomical reduction of fracture, stable internal fixation, experienced surgical team, are crucial factors in acetabular fracture treatment. Early definitive osteosynthesis of the acetabulum is crucial for achieving anatomical reduction of fracture [25,26]. We had an anatomical reduction in 85.71% cases after definitive osteosynthesis of acetabular fracture which was done in a time interval average of 5.09 days from the injury. Two weeks after the injury, it is considerably harder to achieve anatomical reduction, which is crucial for good treatment. Cahueque et al. recommend definitive osteosynthesis of acetabulum up to 7 days from the injury. Same authors describe incidence of 48% of post- traumatic OA within 2 years from the injury [27]. Steven et al, report about the importance of early definitive osteosynthesis of acetabulum as well [28]. Post- traumatic OA accompanies acetabular fractures and is usually associated with nonanatomical fracture reduction [29]. Meena et al. published that not achieving anatomical reduction, associated injuries, initial dislocation, > 20mm, hip dislocation, late definitive osteosynthesis of acetabulum, age, can negatively affect the achievement of good outcome [25]. According to the Matta, the number of anatomical reductions decreased as time to surgery increased [30]. AVN of the femoral head causes latter fragmentation and collapse of the

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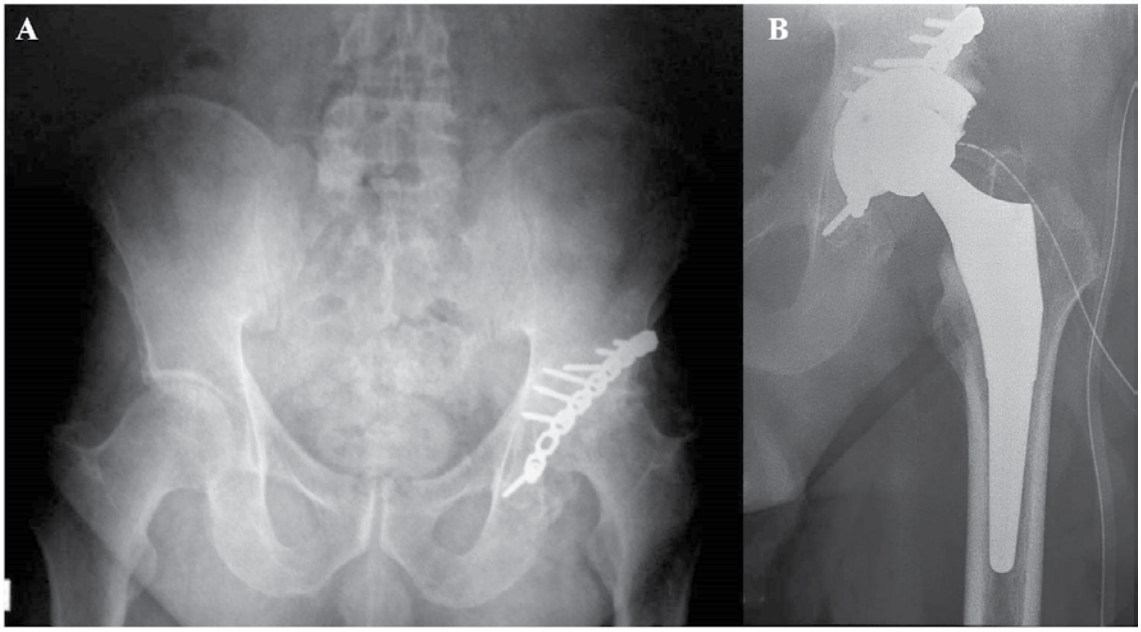

Figure 7 (AB). *THA after previous acetabular surgery. A- X- ray, male 56 years- old ,4 years after the posterior fracture- dislocation of the acetabulum, shows the post- traumatic OA; B- X- ray after uncemented THA.*

head and post- traumatic OA with severe problems which are manifested in the form of severe pain, hip contracture, requires further surgery - total hip arthroplasty (THA). According to Rollmann et al. about 20% of the patients with acetabular fractures require THA [7]. Pavelka et al. published 32.81% post- traumatic OA, 24 months post acetabular fracture [31]. Cahueque et al. published 48% OA, after 2 years from the acetabular fracture [27]. According to Dunet et al., 34.7% of the patients after acetabular fracture required latter THA [32]. Our results show that 36.5 % of the patients required THA due to post- traumatic OA and AVN of the femoral head. Although in 85.71% of the cases we had achieved an anatomical reduction of fracture, we achieved excellent and good final functional results in 76.18%. There are other authors who believe that post- traumatic OA occurs several years after the injury, despite anatomical reduction, which only confirms the importance and severity of acetabular fracture and the anatomical specificity of acetabulum and hip joint [33]. Acetabular surgery will still represent the challenge for surgeons in the future with an uncertain final outcome. The future of the acetabular trauma will still remain in understanding the fundamental principles of acetabular surgery. The principles introduced by Judet and Letournel have yielded positive clinical results and have stood the test of time. In this particular specialty of surgery, no technology can substitute for the human brain - the surgeon's 3- dimensional understanding of the biological approach, the bony anatomy, the fracture pattern, and the reduction and fixation techniques via the exposure. Despite the increase in education, there is no substitute for experience in treating these injuries [6]. Unfortunately, although we have increased the number of orthopaedic surgeons, there is a still small number of orthopaedic surgeons who are familiar with acetabular trauma. Additional continuing education and surgical experience are crucial in the treatment of acetabular fractures. Matta and Merritt have shown that surgical experience is in direct correlation to achieving excellent and good results in the treatment of acetabular fractures [34].The question is, how many acetabular fractures should be surgically treated on a monthly basis, by one experienced surgeon in order to maintain a "surgical training"? Acetabular fractures are not very common. According to Rinne et. al. the incidence of acetabular fractures in Finland was

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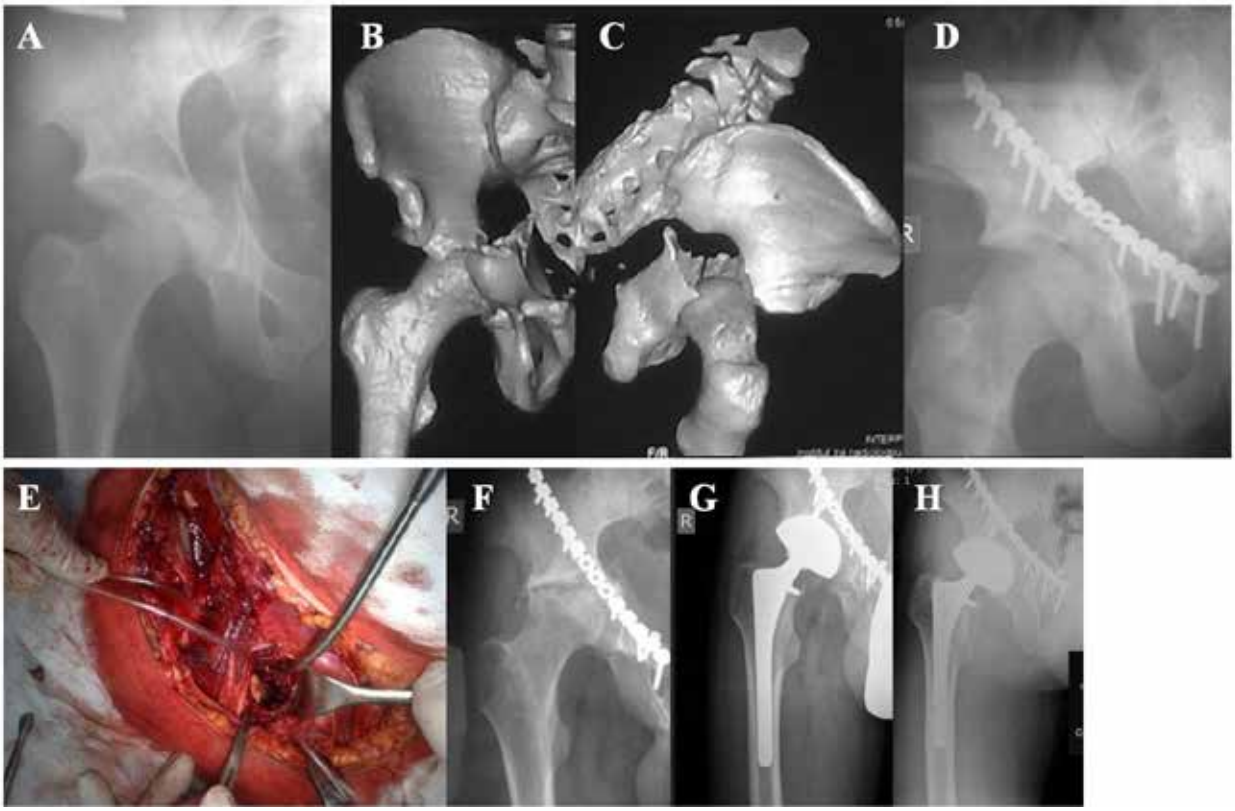

Figure 8(A-H). *THA after previous acetabular fracture and osteosyntheis. A- Transverse acetabular fracture- X- ray; B,C- 3D- CT; D- X- ray after acetabular osteosynthesis; E- Intraoperative view- Ilio-inguinal surgical approach; F- AVN of the femoral head and seondary OA, 4 years after acetabular surgery- X- ray; G- Uncemented THA , 4 years after the injury- X- ray; H- X-ray, 7 years after surgery.*

6.4/100 000 persons/year to 8.1/100 000 persons/year from 2007 to 2014 [35]. According to Laird and Kaeting, it was 3 patients/100 000/year [36]. Mauffrey et al. published similar results [37]. City of Nis is the largest city of the Nisava district, with a population of about 350 000 inhabitants and a tertiary health institution where patients with acetabular fractures are being taken care of. An incidence of about 4 patients /100 000/ year, requires the existence of an experienced surgical team for the treatment of acetabular fractures due to the fact that about 2 500 000 inhabitants of Southern and Eastern Serbia gravitate towards this institution.

Conclusions

Acetabular fractures are uncertain when it comes to the final outcome. Urgent reduction of a dislocated hip, early osteosynthesis of acetabulum, anatomical reduction and surgical experience is crucial for achieving good outcome. Unfortunately, despite following the principles of modern treatment, these severe injuries are followed by complications and will continue to be in the future. Although they cannot be avoided, by continuous learning and improving on the acetabular surgical field, we can achieve more of the excellent and good treatment results and less complications. We do not have an influence on the severity of the initial trauma, general condition of the patient and age, bone quality, and those are just some of the factors which have an effect on the final functional outcome and complications. Given the specifics, acetabular fractures require treatment only in tertiary care facilities.

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Author Contributions

Sasa Milenkovic: conceptualization and writing of the manuscript. Nenad Ilic: data collection, analyzed, interpreted the data and revised the manuscript. Milan Mitkovic: conceptualization, review, and supervision. All authors have reviewed, revised, and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

All patients gave written informed consent.

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The effect of a pharmaceutical per os supplement based on methylsulfonylmethane, hydrolyzed collagen, bromelain, D-glucosamine, chondroitin sulfate, L-arginine, L-lysine, plant extracts of boswellia, myrr and turmeric, and Vitamin C on Achilles tendinopathy

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ABSTRACT

This is a prospective clinical study in order to evaluate the effect of nutraceutical treatment of Achilles tendinitis. Recreational and professional athletes with acute Achilles tendinitis were recruited and divided into a Treatment (n=8) and a Control (n=8) group. Treatment group received food supplement based on Methylsulfonilmethane (MSM), Collagen, Arginine, Lysine, Vitamin C, Glucosamine and Chondroitin sulfate, Boswellia, Curcumin (turmeric acid) and Myrrh for a month. Subjective (VAS score) and objective (VISA-A and Ankle-Hindfoot scales) were evaluated. The Treatment group demonstrated statistically significant pain relief (VAS) at 1st month and better functional outcomes (VISA-A) compared to Control group. It seems that administration of nutraceuticals additional to any other conservative or surgical intervention enhance the final outcome in Achilles tendon pathologies.

KEYWORDS: Food supplements, Achilles tendinitis, Achilles tendinopathy

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Introduction

Terminology

Achilles tendon pathologies can either be due to an acute injury, mostly occurring in relation to sports, or have a chronic background. Acute traumatic loading of the Achilles tendon is associated with acute inflammatory reaction of its paratenon called *Achilles tendinitis.* Cyclic chronic loading during walking or running activities may lead to repetitive microtrauma of the tendon substance and alterations of the tendon microcirculation. Accumulation of chronic microdamage to the tendon itself will cause degeneration of its substance called *Achilles tendinosis*. Degeneration and calcification of the tendon insertion into the calcaneus bone is referred as *Achilles enthesopathy*. It is caused either due to systematic pathology such as autoimmune disorders especially ankylosing spondylitis and psoriatic arthritis or due to repetitive local microtrauma such as in long distance runners. The last two types of chronic Achilles pathology are placed under the general term of *Achilles tendinopathy*. (1-3)

Current treatment options

All the above-mentioned pathology of Achilles tendon is expressed predominately with pain followed by swelling and stiffness. Achilles tendinopathy initial treatment is often conservative, and the available therapeutic options are based on sparse evidence, including physiotherapy, splinting, taping, cryotherapy, extracorporeal shockwave therapy (ESWT), peritendinous injections with corticosteroids or Platelet Reach Plasma products (PRPs), non-steroidal anti-inflammatory drugs (NSAIDs) and food supplements. (4-8)

The role of food supplements in Achilles tendinopathy regarding pain relief and function improvement has not yet been clarified. In a clinical trial, a statistically significant improvement of pain, in terms of Visual Analog Scale (VAS) and Ankle-Hindfoot Scale (AHS) was observed in patients treated with methylsulfonylmethane, collagen, bromelain and vitamin C in association with ESWT compared to ESWT alone. (9)

Study target

Given the known adverse events of prevalent pharmacological treatments for pain such as NSAIDs, and the poor results of local infiltration with corticosteroid and PRP products, we intended to assess the effect of food supplements based on methylsulfonylmethane, collagen and arginine on pain and function in acute cases of Achilles tendinitis in addition to the standard of care. It is the senior author's belief that chronic cases of Achilles tendinopathy are refractive to any conservative treatment alone. In such cases, conservative therapies could be adjuvant to surgical treatment.

Patients and Methods

Design, Setting and Recruitment

This is an arm of an observational non-interventional prospective multicenter international study conducted in ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy with satellite centers in Greece, Spain and Romania. However, due to the COVID-19 pandemic, the multicenter study was not accomplished, so we used our data in the Hellenic population. Patients were recreational or professional long distance runners recruited at the 5th Orthopaedic Department, Hygeia Hospital in Athens, Greece.

Food supplement was based on Methylsulfonilmethane (MSM), Collagen, Arginine, Lysine, Vitamin C, Glucosamine and Chondroitin sulfate, Boswellia, Curcumin (turmeric acid) and Myrrh. The supplement was offered by the Hellenic branch of Galenica Pharmaceutical Industry under the commercial name of *Tendisulfur Forte*. The usual course of treatment was two drug sachets daily for 30 days according to information provided by the manufacturer. Each sachet contained Methylsulfonilmethane 5000 mg, Collagen 2000 mg, Arginine 2000 mg, Lysine 1000 mg, Vitamin C 1000 mg, Glucosamine 300 mg , Chondroitin sulfate 300 mg, Boswellia 200 mg, Curcumin 200 mg and Myrrh 100 mg. Subjects who participated according to the authors' judgement and the current clinical practice, were divided into two groups: **group-A (Treatment Group)**, who received the treatment (n=8) and **group-B (Control Group)**, who were not offered (placebo) or who refused the treatment (n=8). Initially, 20 patients were recruited, however four of them were excluded due

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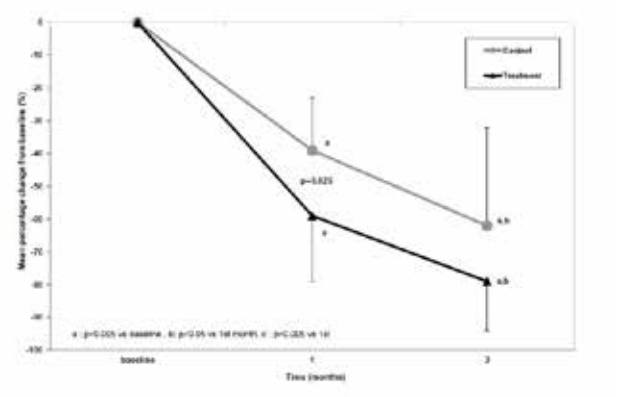

Figure 1. *Visual Analogue Scale (VAS) during the observation period*

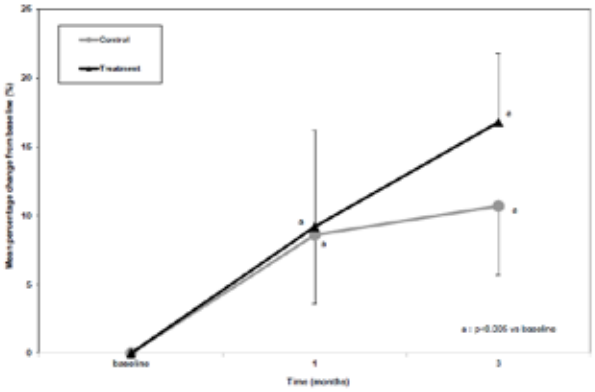

Figure 2. *The Victorian Institute of Sport Assessment-Achilles Questionnaire (VISA-A) during the observation period.*

to non-compliance with the appropriate treatment. The intake of NSAIDs, paracetamol and other painkillers, was considered as concurrent treatment(s) at the doses indicated on the product information and according to the attending physician's judgement.

Endpoint and outcome measures

This study had a duration of 10 months of which 4 months were needed to complete the enrolment. The patients' symptoms were followed over a period of 2 months, with a total of 4 visits (baseline visit, 15 days, 30 days, and 60 days). The subjective outcome was to assess the effect (30-day average change) of the treatment on pain from Achilles tendinitis measured by VAS pain (0-100 horizontal line) in subjects who received the treatment compared to who did not. The objective outcome assessed the effect (15-, 30- and 60-day average changes) of the treatment on pain from Achilles tendinitis measured by patient-reported outcomes (VISA-A questionnaire and Ankle-Hindfoot Scale) in subjects who received the treatment compared to who did not. (10-12)

Inclusion criteria

All patients were above 18 years old. The diagnosis of Achilles tendinitis was based on the presence of the clinical criteria: the subjective reporting of pain and/or pain on palpation of the tendon with a duration < 3 months either mono- or bilaterally and VAS pain when walking > 30/100

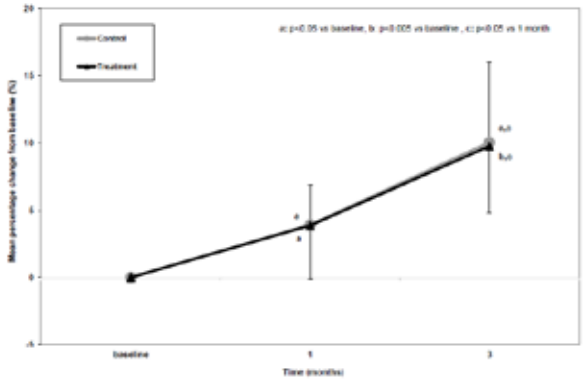

Figure 3. *The Ankle Hindfoot Score (AH) during the observation period*

Exclusion criteria

Patients with: (a) acute (<6 weeks) traumatic Achilles tendinopathy, (b) diagnosis of complete or partial rupture of the Achilles tendon, (c) diagnosis of spondyloenthesoarthritis (ankylosing spondylitis) or psoriatic arthritis, and (d) congenital or acquired deformities of the lower limbs, were excluded. Additionally, patients with (a) history of Achilles tendon surgery; (b) paratendinous injections (local anesthetics and/or corticosteroids) administered within the previous 4 weeks; (c) the administration of the same components of the treatment within the

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TABLE 1.

Homogeneity between groups

	Control	Treatment	p-value
Age (years)	48.80±6.92	52.18±13.05	0.474
Gender, male/female; n (%)	1(10.0)/9(90.0)	0(0)/ 11(100.0)	0.476
Height (cm)	177.00±3.02	181.00±7.40	0.122
Weight(kg)	71.20±6.20	78.73±9.40	0.045
BMI	22.68±1.33	24.01±2.26	0,124
Quinolones, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Paracetamol, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
NSAID, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Food supplement, no/yes; n (%)	9(90.0) / 1(10.0)	7(63.6)/ 4(36.4)	0.311
Metabolic syndrome, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Alcohol, no/yes; n (%)	10(100.0) / 0(0)	11(100.0) / 0(0)	1.000
Physical exercise, amateur/prof; n (%)	8(80.0)/2(20.0)	11(100.0) / 0(0)	0.214
Lab exams, normal/abnormal; n(%)	10(100.0) / 0(0)	8(72.7)/3(27.3)	0,214
Site, right/left; n (%)	7(70.0)/ 3(30.0)	8(72.7)/3(27.3)	1.000

All values are presented as mean±SD

previous 3 months; (d) chronic (≥ 3 months) glucocorticoid therapy (≥5 mg prednisone equivalent daily); (e) cryotherapy and/or (f) ESWT performed within the previous 3 months or planned in the following 10 weeks, were also excluded.

Statistical analysis

Data were expressed as mean±standard deviation (S.D.) or median (in case of violation of normality) for quantitative variables and as frequencies, percentages for qualitative variables. The Shapiro-Wilks test was utilized for normality analysis of the parameters. The homogeneity between groups examined using the independent samples t-test and Fisher's exact test. The comparison of variables at each time point was performed using the independent samples t-test or Mann-Whitney test in case of violation of normality. One factor Repeated Measures ANOVA model was used for the comparison of different time measurement of variables for each group. Pairwise multiple comparisons were performed using the Bonferroni test.

The efficacy of the treatment during the observation period was evaluated by calculating the mean percentage changes from baseline after 1 and 3 months respectively. Comparison of percentage change from baseline of parameters during the observation period between 2 groups was analyzed using the independent samples t-test.

All tests were two-sided and statistical significance was set at $p < 0,05$. All analyses were carried out using the statistical package SPSS vr 21.00 (IBM Corporation, Somers, NY, USA).

Results

There was homogeneity between compared groups for all demographic and clinical characteristics ($p>0.05$). (**Table 1**)

At the baseline measurement of the VAS scale, (**Fig.1, Table 2**) the 2 groups had no statistically significant difference ($p=0.595$) but Treatment group presented statistically significant lower VAS

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TABLE 2.

Comparison of VAS between groups during the observation period

Group	Baseline	1 month	3 months	p-value$_{wg}$	% change baseline-1m	% change baseline-3m
Control	48,50±17,96	30,00±13,33 [b]	21,50±18,26 [b,c]	<0.005	-39,00±16,41	-61,89±32,31
Treatment	44,55±15,56	16,36±8,10 [b]	8,64±6,74 [b,d]	<0.005	-59,10±21,34	-79,34±15,66
p-value$_{bg}$	0,595	**0,010**	**0,042**		**0,026**	0,126

bg : between groups , wg : within groups

All values are presented as mean±SD

p-value$_{bg}$, p-value between groups ; p-value$_{wg}$, p-value within groups.

[a]p<0.05 vs baseline, [b]p<0.005 vs baseline

[c]p<0.05 vs 1 month, [d]p<0.005 vs 1 month

at 1st month (p=0.010) and 3rd month (p=0.042) respectively compared to Control group. Statistically significant differences in the percentage change of VAS from baseline to 1 month were detected between Control and Treatment groups [-39.0%±4.27 vs -59.10%±21.34; p=0.026]. For the Control group, VAS statistically significantly decreased from baseline measurement to 1 (p=0.002) and 3 (p<0.005) months respectively. Moreover, additional decrease was presented between 1st and 3rd month (p=0.009). For the Treatment group, VAS statistically significantly decreased from baseline measurement to 1 (p=0.001) and 3 (p<0.005) months respectively. Moreover, additional decrease presented between 1st and 3rd month (p=0.003).

The 2 groups had no statistically significant difference at baseline (p=0.373), 1st month (p=0.346) and 3rd month (p=0.805) respectively for VISA-A scale. (**Fig.2, Table 3**). No statistically significant differences in the percentage change of VISA from baseline to 1st month [8.58%±5.12 vs 9.19%±7.42; p=0.827] and 1st month [10.65%±5.52 vs 16.79%±11.93; p=0.146] were detected between Control and Treatment groups. For the Control group, VISA-A statistically significantly increased from baseline measurement to 1 (p<0.005) and 3 (p<0.005) months respectively. For the Treatment group, VISA-A statistically significantly increased from baseline measurement to 1 (p=0.003) and 3 (p=0.001) months respectively.

The 2 groups had no statistically significant difference at baseline (p=0.067), 1st month (p=0.100) and 3rd month (p=0.189) respectively for AH score. (**Fig.3, Table 4**) No statistically significant differences in the percentage change of AH from baseline to 1st month [3.92%±3.66 vs 3.87%±4.38; p=0.977] and 1st month [10.05%±6.32 vs 9.78%±5.54; p=0.918] were detected between Control and Treatment groups. For the Control group, AH statistically significantly increased from baseline measurement to 1 (p=0.002) and 3 (p=0.003) months respectively. Moreover, additional increase presented between 1st and 3rd month (p=0.055).For the Treatment group, AH statistically significantly increased from baseline measurement to 1 (p=0.033) and 3 (p<0.005) months respectively. Moreover, additional increase presented between 1st and 3rd month (p=0.014).

Discussion

Achilles tendon pathology is a very common disease with a rising incidence due to sport activities, life expectancy, environmental and dietary factors, some drug therapies and systemic disorders. Not only athletes, but also the general and elder populations suffer from post-traumatic, overuse, inflammatory or degenerative tendinopathies. It seems that the combination of anatomical (tendon quality) and functional (mechanical overuse) factors leads to the development of the Achilles pathology. (1,3)

Histological studies have evaluated the disturbed matrix metabolism in Achilles tendinopathies. An imbalanced MMP/TIMP expression and highly increased collagen expression, seems to be the

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TABLE 3.

Comparison of VISA between groups during the observation period of 3 months

Group	Baseline	1 month	3 months	p-value$_{wg}$	% change baseline-1m	% change baseline-3m
Control	73.00±10.77	79.00±10.83 [b]	80.60±11.88 [b]	<0.005	8.58±5.12	10.65±5.52
Treatment	68.73±10.69	74.64±9.87 [b]	79.45±9.05 [b]	<0.005	9.19±7.42	16.79±11.93
p-value$_{bg}$	0,373	0,346	0,805		0,827	0,146

bg : between groups , wg : within groups

All values are presented as mean±SD

p-value$_{bg}$, p-value between groups ; p-value$_{wg}$, p-value within groups.

[a]p<0.05 vs baseline, [b]p<0.005 vs baseline

[c]p<0.05 vs 1 month, [d]p<0.005 vs 1 month

TABLE 4.

Comparison of AH between groups during the observation period of 3 months

Group	Baseline	1 month	3 months	p-value$_{wg}$	% change baseline-1m	% change baseline-3m
Control	78.00±5.42	81.10±6.79 [a]	85.90±8.58 [a,c]	<0.005	3.92±3.66	10.05±6.32
Treatment	82.64±5.48	85.73±4.92 [a]	90.73±7.64 [b,c]	<0.005	3.87±4.38	9.78±5.54
p-valuebg	0,067	0,100	0,189		0,977	0,918

bg : between groups , wg : within groups

All values are presented as mean±SD

p-value$_{bg}$, p-value between groups ; p-value$_{wg}$, p-value within groups.

[a]p<0.05 vs baseline, [b]p<0.005 vs baseline

[c]p<0.05 vs 1 month, [d]p<0.005 vs 1 month

most important characteristic in tendinopathy and chronic ruptured tendons. On the other hand, in acute rupture cases, other mechanisms such as inflammation and innervation as indicated by CD45 and CD68 positive cells and the expression of inflammatory cytokines and nerve markers, seem to play a more important role. (13)

Targeting the disturbed matrix metabolism or - event better - preventing the inflammatory cascade seems to be a very attractive therapeutic approach for Achilles tendon pathologies. (**Table 5**) Recently, the use of oral supplements has been proposed to support the physiological turnover of tendon tissue, in order to prevent inflammation and degeneration. Such oral supplements, also mentioned as *nutraceuticals*, involve glucosamine and chondroitin sulphate (GlcN-CS), vitamin C (vit C), hydrolysed type 1 collagen (Col 1), L-arginine alpha-keto-glutarate (AAKG), curcumin, boswellic acid (BA), methylsulfonylmethane (MSM), and bromelain. Increasing the concentration of these compounds in tendon context may help to preserve, or even repair, the damaged tendons. As food supplements, these are not subjected to rigorous controls and licensing processes as drugs; even if some of these products received permissions to be commercialized as drugs in many countries. An amount of pre-clinical studies and randomized controlled trials (RCTs) have been conducted to assess the effectiveness of oral supplements in the management of tendinopathies. (14)

Sandqvist et al, compared Glc-Nor indomethacin

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TABLE 5.

Overview of principal nutraceutical and their properties (14)

Nutraceutical	Biological effect
Glucosamine and chondroitin sulphate (GlcN-CS)	Increase collagen synthesis, ameliorate mechanical properties, organization of collagen bundles and resistance to fatigue, helpful in the management of pain.
Vitamin C (Vit C)	Stimulate hydroxyproline synthesis of procollagen, enhance angiogenesis and maturation of Col III to Col I fibers, anti-inflammatory and antioxidant effect.
Collagen I (Col I)	Increase mechanical properties, beneficial effects on collagen-rich tissues.
L-arginine-α-keto-glutarate	Substrate of NOS, increase NO levels and collagen synthesis.
Curcumin	Neo-angiogenesis and apoptosis inhibitor, antioxidant effect, stimulate tenocytes survival.
Boswellic acid	Elastase and 5-LO activity inhibition, reduce TNFα, IL-1, IL-2, IL-4, IL- 6 e INFγ levels.
Methilsulfonilmethane (MSM)	Analgesic, anti-inflammatory and antioxidant effects, reduce MDA and GSSG levels.
Bromelain	Decrease lymphocytes rolling, anti-edema, antioxidant and immunosuppressive effects, reduce MDA levels.

** Glc-N-CS: glucosamine and chondroitin sulphate; vit C: vitamin C; Col I: collagen type 1; Col III collagen type 3; AAKG: L-arginine-α-keto-glutarate; NOS: nitric oxide synthase; NO: nitric oxide; 5-LO: 5-lipoxygenase; TNFa: tumor necrosis factor a; IL-1/2/4/6: interleukin 1/2/4/6; IFNγ: interferon γ; MSM: methilsulfonil methane; MDA: malonyldialdehyde; GSSG: oxidized glutathione).*

administration in the management of Achilles peritendinitis showed that Glc-N had a better overall therapeutic effect on 2/3 of the patients compared to 1/3 of the patients treated with Indomethacin. Especially in those patients who endure a persistent pain, Glc-N proved to be more effective than indomethacin. Also non-responders to Indomethacin showed a little/moderate benefit from Glc-N therapy on pain level. (15)

Notarnicola et al, tested the effect of nutraceutical supplementation (L-arginine-α-cheto-glutarate, vinitrox™ (a polyphenolic compound), MSM, bromelain, type 1 collagen, and vitamin C) and extracorporeal shockwave therapy in patients with insertional Achilles tendinopathy. The authors reported that the combined treatment lead to a lower level of pain and better results at Ankle-Hindfoot scale, and Roles/Maudsley score than extracorporeal shockwave therapy alone. (9)

Arquer et al, valuated a commercial available dietary supplement containing mucopolisaccharides, type 1 collagen, and vitamin C in the management of Achilles, patellar, and common extensor tendons tendinopathies. The overall showed an improvement of symptoms and structural evolution of injured tendons. Patients treated with the oral supplementation for 90 days showed a reduction of pain and a functional improvement already after 10 days. At 90 days they demonstrated a significant improvement of functional scales: 38% for Achilles, 46% for patellar and 77% for common extensor tendons, and also a reduction of tendon thickness from 10 to 20%, depending on the anatomical region. (16)

Merolla et al, assessed the analgesic effect of Tendisulfur (GlcN-CS, vitamin C, type 1 collagen, L-arginine-α-keto-glutarate, BA, curcumin, and MSM) in patients with a full-thickness supraspinatus tendon rupture treated arthroscopically. Patients were randomly assigned to dietary supplement or placebo for 2 months. After 1 week, treatment group showed significantly lower level of VAS, night pain and pain after activity. Constant-Murley score and simple shoulder test (SST) did not differ between the 2 groups. Patients also reported a good global assessment and no adverse effects. However, after 2 weeks all scores presented no significant differences, even if pain values were lower. The authors

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concluded that Tendisulfur alleviated short and partially mid-term pain, but did not affect long term pain. To solve this limitation, they suggested to increase dosage over the first 4 weeks and by extending treatment by 1 or 2 months. (17)

In our study, the use of Tendisulfur Forte (Methylsulfonilmethane, Collagen, Arginine, Lysine, Vitamin C, Glucosamine and Chondroitin sulfate, Boswellia, Curcumin and Myrrh.) in recreational and professional athletes with acute Achilles tendinitis showed satisfactory results regarding pain and function of the tendon. The subjective VAS pain score was significantly improved in both groups from baseline to 1 month when the treatment ended. The score continue improving for both groups up to 3 months when the observation period ended. However, The VAS score was statistically significantly better for the Treatment group at 1 month and significantly better for the Treatment group at 3 months. These data suggest that Tendisulfur Forte alleviates pain rapidly at the short term period and continues offer relief even after the end of its administration. Regarding the objective outcomes, the VISA-A questionnaire score was improved in both groups at 1 and 3 months. However, the Treatment group demonstrated much better results at 3 months when compared to Control group. It is the authors' impression that extending the treatment beyond one month, we would have had statistically significant better VISA-A scores when compared to Control group. Finally, the Ankle-Hindfoot scale was significantly increased in both groups but with no differences between the groups. All above findings suggest that Tendisulfur forte contributes strongly to pain relief and mildly to function of the affected Achilles tendon. A longer period of treatment would probably offer better functional results and enhance the rehabilitation of the patient. Since such nutraceuticals are not doing any harm, patients suffering from Achilles tendinitis or tendinopathy would benefit by taking supplements such as Tendisulfur Forte during the period of rehabilitation and additionally to any other conservative or surgical intervention.

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REVIEW

The role of JAK1/2 kinases in the development of neurogenic heterotopic ossification following spinal cord injury

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ABSTRACT

Neurogenic heterotopic ossification is a complex disease that is characterized by the formation of heterotopic bone in soft tissues following central nervous system injuries and various neurological disorders. The exact mechanism of the disease and the factors that play a role in its development are still unknown and they comprise a promising research field. However, understanding the pathophysiology of the disease can lead us to diagnosis and help us find more effective ways of treatment.

The JAK-STAT signaling pathway is a mechanism of cellular signaling that is involved in many processes of the organism, such as the development of the skeletal system and the regulation of the neuroinflammatory response that follows spinal cord injuries. The purpose of this study is the research of the bibliography concerning the role of these JAK1 and JAK2 tyrosine-kinases in the development of neurogenic heterotopic ossification following spinal cord injuries.

KEY WORDS: Neurogenic heterotopic ossification, spinal cord injuries, JAK-STAT, JAK1, JAK2

Introduction

Heterotopic ossification, or *de novo* bone formation, represents pathologic condition during which benign, mature, lamellar bone is formed in tissues which do not belong in the skeletal system. Heterotopic bone formation is observed in tissues with high concentration of connective tissue cells (i.e. periosteum, peritenon, perimysium). Ectopic bone

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has also been observed in the walls of blood vessels, ligaments and even in tissues of the abdomen [1-9].

In general, heterotopic ossification can be divided into three categories, depending on the etiology behind its formation: (a) traumatic, (b) neurogenic and (c) genetic [1,2,4-6,9,10]

Neurogenic heterotopic ossification is a type of *de novo* bone formation which best describes the cases of heterotopic bone formation following Central Nervous System (CNS) trauma, such as traumatic brain injuries (TBI) or spinal cord injuries (SCI). There is an ongoing debate as to the mechanisms and factors that play a role in the development of the disease. Nowadays, the role of JAK-STAT signaling pathway in the pathogenesis of the disease has been investigated due to its involvement in the neuroinflammatory process that follows spinal cord injury. This review will primarily focus on neurogenic heterotopic ossification following spinal cord injury and the role of JAK1/2 kinases.

A thorough literature search was performed using the 'PRISMA' systematic review guidelines and in the PubMed database using the key words "heterotopic ossification", "neurogenic heterotopic ossification", "JAK-STAT & spinal cord injury" and "JAK-STAT & heterotopic ossification". We limited our search to articles written in the English language and published from 1990 to 2020. The search yielded 7201 results in total. Removal of duplicate articles, resultied in 7071 articles of which 6965 were excluded since they weren't relevant to this review. The full text articles of the remaining 106 records were then investigated for eligibility and 50 of those were excluded for various reasons, leaving 56 articles for the synthesis of this review. There is abundant literature that highlights the role of JAK1and JAK2 proteins in various physiological processes but there is only one article that highlights the role of those tyrosine kinases in the formation of neurogenic heterotopic ossification following spinal cord injury (Table 1).

Discussion

The pathophysiology of Neurogenic Heterotopic Ossification

Neurogenic heterotopic ossification occurs in patients that have sustained traumatic brain and spinal cord injuries. Rarely, it may also occur in patients with Guillain-Barré syndrome, as well as in cases with tumors or hemorrhage of the central nervous system. Additionally, patients suffering from meningitis, myelitis, multiple sclerosis or are comatose for a long period of time also risk developing neurogenic heterotopic ossification [11-19]

The pathophysiology of heterotopic ossification is not clearly understood, even today, due to the complexity of the disease. In recent years, thanks to various research studies on Fibrodysplasia Ossificans Progressiva, progress has been made in understanding the mechanisms behind its appearance and we now know that various systemic and local factors play a role in its pathogenesis. In various studies, the local induction properties of Bone Morphogenetic Proteins –BMPs has been noted, as well as the systemic effect of prostaglandin E2 -PGE2. According to the bibliography, despite the existence of some common cellular mechanisms between Fibrodysplasia Ossificans Progressiva and the acquired types of heterotopic ossification, a unifying mechanism has not been found yet. It is important to note that the pathophysiology of the disease bears some similarities to the normal fracture healing process, making heterotopic ossification an obstacle when it comes to the treatment of orthopaedic patient [1,3,6,7,20–22]

Normal bone formation requires inductive signaling pathways that consist of chemokines, cytokines, bone morphogenetic proteins, growth factors, prostaglandins, interleukins, inductive osteoprogenitor cells and a permissive osteoinductive environment. Moreover, a proper quantity of osteoclasts which are responsible for the metabolic changes observed in normal bone, so that the skeletal system can adapt to various changes such as development and growth due to physical activities. During the normal bone development process, bone is formed after multipotent osteoprogenitor cells migrate, proliferate and differentiate. This process seems to bear some similarities to the pathological bone formation process that has been observed in cases of heterotopic ossification. It is also important to note that the heterotopic bone is similar to normal bone in

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some aspects but it does not have a periosteum and a high concentration of osteoblasts and osteoclasts. This type of bone is characterized by high biological activity and increased formation rates [1,3,6,7,20-22]

Recently, experimental studies have revealed certain mechanisms and molecules involved in the bone formation process of neurogenic heterotopic ossification and have led to the development of theories for the pathophysiology of the disease. The main theory comes from the observation that the serum of patients that sustained central nervous system injuries, when in contact with osteoprogenitor muscle cells, inducts mitosis and shows osteogenic properties. Debaud *et al,* developed an animal model where mice with thoracic spinal cord were injected with the snake poison cardiotoxin, to promote an inflammatory reaction. They reported that inflammation of the nervous system, due to peripheral trauma, leads to an increase of the heterotopic bone that is formed thus proving a correlation between neurogenic heterotopic ossification and abnormal molecular signaling. This theory supports that central nervous system injuries lead to a release of signaling molecules that interact with local and circulating progenitor cells, leading to their proliferation and differentiation to osteoblasts and finally to the formation of heterotopic bone. Three factors have been proven to be important in the pathophysiology of the disease and seem to mimic the stages of the normal fracture healing process: osteogenesis, osteoinduction, and osteoconduction) [1,3,6,7,11,13,15-18,20-28].

Inflammation and spinal cord injury

Central nervous system injuries are the first step in the process that leads to heterotopic bone formation, as they induce an inflammatory response. Three different stages can be distinguished: (i) the acute phase, (ii) the secondary and (iii) the chronic phase. The acute phase refers to the immediate tissue damage and usually lasts a few days. Mechanical injury leads to lesions of the nervous system and ischemia due to limited blood supply. The secondary phase refers to the inflammation process that follows the abnormal release of neurotransmitters and the subsequent damage to the tissues. In this stage, oxidative stress is often observed due to the established ischemia and the release of molecules related to inflammation. The chronic phase includes the Wallerian degeneration and the formation of scar tissue since healing is often incomplete, and the continuation of the cell apoptosis. The inflammatory response involves cells of the nervous system as well as cells recruited from the periphery [29-34].

Central nervous system has its own system of immunological response due to the presence of the blood brain barrier and the blood spinal cord barrier. Several studies support that there are lymphatic vessels in the blood spinal cord barrier that connect the central nervous system and the peripheral nervous system and during inflammation a migration of cells from the latter to the first one is observed. Important cells of the inflammatory process of the central nervous system are the microglial cells. Activation and proliferation of these cells results in the production of cytokines and recruitment of WBCs from the periphery to induce phagocytosis of injured tissues. Astrocytes are another type of central nervous system cells that participate in the inflammation process and are responsible for the recruitment of microglial cells. Astrocytes produce cytokines, such as CCL2, CXCL1, CXCL2, CXCL10, GM-CSF and IL-6, and recruit cells from the periphery. They are also responsible for the regulation of homeostasis. Other central nervous system cells are the oligodendrocytes that are responsible for the axonal myelin. They are part of the inflammatory response and they are sensitive to damage, leading to pathological conditions since inflammation induces autoimmunity against myelin. During inflammation oligodendrocytes precursor cells migrate to the point of damage [29,30,33-35]

Neutrophils are an example of cells that are recruited from the periphery during the inflammatory response, reaching maximum concentration after 1-3 days. These are phagocytic cells and secrete cytokines that help activate other immune cells. Macrophages are another type of cells that are recruited from the periphery. These cells exhibit different phenotypes, determined by their environment, adapt to the different stimuli and participate in the wound healing process. Macrophages exhibit two pheno-

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types during inflammation, M1 and M2, and their transcription is a complicated process with different factors regulating each type. M1 macrophages' transcription is regulated by STAT1, IRF-5 while M2 is regulated by STAT6, IRF-4 and PPARs. PPARs are transcription factors expressed in microglial cells, astrocytes, neurons and oligodendrocytes [29,30,33-35]. M1 macrophages, combined with endogenous microglial cells, express cytokines, such as TNF-α, IL-6, IL-12, and IL-1β, which induce CD4+ T cells that are responsible for both the phagocytosis of damaged cells and the recruitment of new neutrophils. At this stage, M2 macrophages express arginase-1 and Ym1 and there is an increase in markers such as IL-4, CD206 and Fizz-1, which are characteristic M2 activation markers. Macrophages and neutrophils also produce reactive oxygen species (ROS) and inducible nitric oxide synthase (i-NOS). These molecules are usually observed under normal conditions but after spinal cord injury or other pathological conditions they induce oxidative stress and neuronal death. Ahn *et al,* showed that apoptosis following spinal cord injury seems to depend on the caspase-3 pathway, activated through PPARs, inhibiting DNA repair processes. Therefore we can conclude that the complex macrophage population that is observed has a dual role as on one hand M1 promote the inflammatory response and phagocytosis and on the other hand M2 have anti-inflammatory properties and promote healing [29,30,33-35]

During inflammation, proliferation and differentiation of oligodendrocyte precursor cells are also observed, as well as astrocyte-driven scar tissue formation and Wallerian degeneration. At this stage M2 macrophages gradually decrease in numbers. Differentiation of oligodendrocyte precursor cells continues but full remyelination of axons isn't observed. It is easy to conclude that normal macrophages' function, during the inflammatory process does not promote full healing of the lesion and that abnormal expression of macrophages can lead to chronic inflammatory conditions and incomplete injury healing [29,30,33-35]

The role of JAK-STAT pathway

The JAK-STAT signaling pathway is a type of conserved cellular signaling which is involved in the processes of cell proliferation, differentiation, migration and the inflammatory response. It was first discovered due to interleukin IL-6 and IFNγ signaling. IL-6, together with IL-11, oncostatin M (OSM), leukemia inhibitory factor (LIF), CT-1 and neurotrophin-1, belong to the gp130 superfamily. Binding of these cytokines to the receptor leads to the homodimerization of gp130 and the activation of the appropriate JAK proteins [36-41].

The JAK protein family consists of four tyrosine kinases JAK1-3 and TYK2, while the STAT family consists of seven proteins STAT1-4, STAT5A/B and STAT6. STAT proteins have 6 regions with conserved structure and function. These six regions include a DNA binding region, an SH2 region and a region for transcription activation (TAD). JAKs have 7 domains with JAK homology (JH1-JH7). JH2 is a pseudokinase region and it is next to JH1. JAK-STAT proteins are expressed in all cells and their specificity is ensured by the variety of cytokines and growth factors that bind to them [36-40].

The JAK-STAT pathway is responsible for signaling processes of the nervous and skeletal system. The interaction between JAK-STAT signaling and the inflammatory process following spinal cord injury is a promising research field. It has been shown that cytokines of the gp130 family are responsible for the induction of inflammation and the activation of the JAK-STAT signaling pathway through JAK1 and JAK2 kinases and STAT1 and STAT3.[29,33,38-40,42-45].

JAK1 and JAK2 are involved in the process of bone formation. Oncostatin M, which belongs to the gp130 family, has the ability to bind to two receptors. Type I receptor consists of gp130 and LIF while the type II receptor consists of the complex gp130 and oncostatin M receptor (OSMR). Oncostatin M is secreted from hematopoietic cells, such as macrophages, neutrophils and dendritic cells and from osteocytes, osteoblasts and microglial cells. It has been shown that oncostatin M is responsible for the induction of mesenchymal spinal cord cells' differentiation to osteogenic cells and the *in vitro* differentiation of osteoblasts. Oncostatin M induces the phosphorylation of JAK1 and JAK2 in osteoblasts

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in animal models, while JAK1 and JAK2 knockout mice die early, either due to weight loss or anemia, prior to bone formation.

Skeletal growth also seems to be affected by STAT1 and STAT3. STAT1 related genes affect the inflammatory process while STAT3 seems to have an anti-inflammatory and pro-proliferation effect. STAT1 deficient mice exhibit higher bone mass and faster fracture healing since STAT1 naturally inhibits the transcription of Runx2 of osteoblasts. On the other hand, STAT3 deletion in mice osteoblasts leads to lower bone mass and inhibition of endochondral ossification, suggesting that STAT3 plays a role in embryonic development and in the processes of cell growth, inhibition of apoptosis and bone homeostasis through regulation of the B-xL, Bcl-2, Fas, Cyclin D1, Survivin and C-Myc genes. STAT3 mutations are associated with abnormal bone growth and increased bone decomposition, which supports the hypothesis that STAT3 promotes osteoblasts' function. There are various studies that suggest that STAT3 is important for chondrocytes' and osteoclasts' differentiation and therefore for the *in vivo* bone formation.[28,31,32,34,36,42,46-50].

The JAK-STAT pathway also seems to be involved in the central nervous system through its role in neurogenesis and scar tissue formation. It has been shown that JAK1,STAT1 and STAT3 are activated in cortical precursor embryonic cells following CNTF receptor activation, inducing the differentiation of neural stem cells and neural progenitor cells into astrocytes, through the gp130 signaling pathway. In general it has been shown that binding of IL-6 leads to the dimerization of gp130 and the subsequent activation of JAK-STAT and phosphorylation of STAT3. Moreover, prolactin induces both differentiation of astrocytes through phosphorylation of JAK2, STAT1, STAT5a and STAT5b [31,33,35,39,42,51,52]

This pathway is also involved in the inflammation process following spinal cord injury. Inhibition of IL-6 receptor inhibits astrocytes' differentiation through JAK-STAT and astrogliosis leading to unhealed axons. It has also been shown that STAT3 inhibition leads to a decrease of active astrocytes, thus affecting barriers of the central nervous system. Leung *et al* showed that STAT3 expression in astrocytes lasted longer after deletion of SOCS3 and wound healing was improved. Astrocytes demonstrate neuroprotective abilities through the release of various cytokines. Among those are IL-6, transforming growth factor β1 and various neurotrophic factors such as NGF, CNTF and b-FGF. Research data supports that, following spinal cord injury, CNTF is produced by astrocytes and leads to phosphorylation of JAK1, JAK2, STAT1 and STAT3. Yamauchi *et al* studied the concentration of JAK1 and STAT3 in accordance to time and they proved that the maximum IL-6 concentration occurs simultaneously with the time point where JAK1 and STAT3 expression was at its maximum. They also showed that JAK1 expression starts immediately after the injury and when it reaches its peak, it gradually decreases, same as IL-6 expression.. Other studies have shown that administration of the inhibitor for miR-21, leads to inhibition of IL-6R/JAK-STAT pathway and better wound healing. Dai *et al,* through the usage of spinal cord injury mice models, noted that there appears to be a correlation between time and the expression of JAK2 and STAT3, which reached a peak after the 10th day post injury. SOCS3, which is a negative regulator of JAK-STAT and is induced by IL-6 cytokines through activation of STAT3, inhibits cellular apoptosis. Oncostatin M induces the activation of STAT3 and the subsequent activation of SOCS3. Experimental studies showed that GM-CSF factors induced activation of JAK2/STAT5 through IL-6, thus affecting cell proliferation and differentiation. On the other hand, use of IFNγ activates JAK2/STAT1 and JAK2/STAT3. All of the above suggest that SOCS3 is an important regulator of JAK-STAT signaling that reduces the risk of inflammation-related complications [16,18,23,26,28,30-32,34,35,38,42,46,47,53-56.]

Various studies that support the role of JAK1 and JAK2 proteins in the function of oncostatin M. Levy *et al* proved that OSM induces phosphorylation of JAK1 and JAK2 kinases and the subsequent activation of STAT1 and STAT3 in osteoblasts, in vitro. Moreover, macrophages activated after spinal cord injury, release oncostatin M among other osteogenic factors. Torrosian *et al* proved that in patients with neurogenic heterotopic ossifica-

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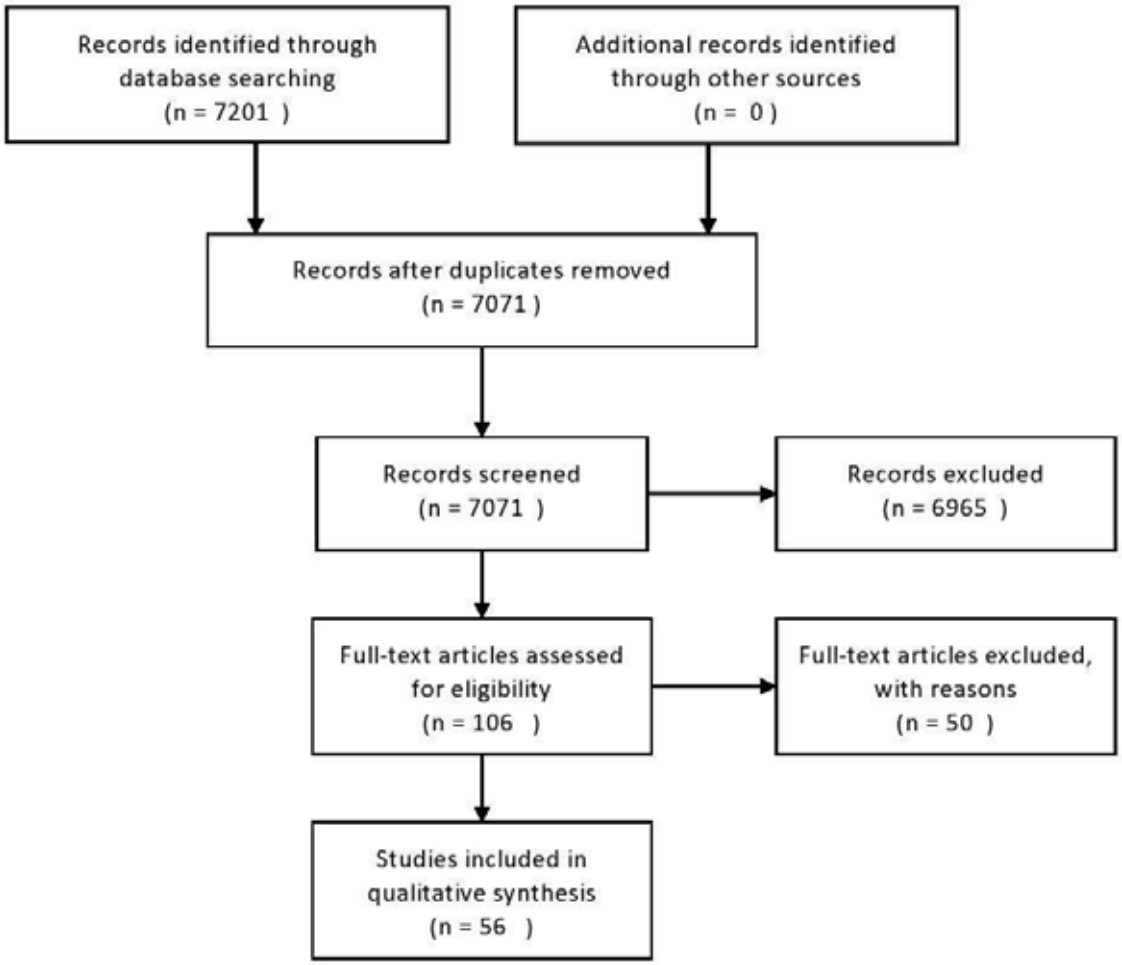
TABLE 1.

Flow diagram showcasing the results of a search in the PubMed database and the selection process for the articles used in this review



tion, activated macrophages induce inflammation through production of high OSM levels and that high plasma OSM concentration can be found in these patients. They also showed that deletion of the OSMR (receptor of OSM) gene in mice leadS to heterotopic ossification inhibition. Alexander *et al.* injected spinal cord injured mice with cardiotoxin and noted that spinal cord injury allows the entrance of monocytes/macrophages in the injured tissue and the production of OSM. Binding of OSM to the receptor promotes phosphorylation of JAK1, JAK2 and activation of STAT3 [16,18,23,26,28,30-32,34,35,38,42,46,47,53-56].

Conclusion

Neurogenic heterotopic ossification is a complex disease which still today is poorly understood. It is characterized by heterotopic bone formation following central nervous system trauma and after certain conditions such as Guillain-Barré syndrome or tumors. Spinal cord injuries are responsible for the formation of neurogenic heterotopic ossification which is observed in 20-30% of cases with such trauma. Heterotopic bone is often formed in the hip region but other areas are also susceptible, such as knees, elbows, shoulders, arms and spine. Spinal cord injury of the thoracic and cervical spine, leads to het-

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erotopic bone formation and ankylosis.

This disease exhibits similarities to the normal bone formation process; however its pathophysiology is not completely understood. Recent data highlight the importance of the inflammatory process that follows spinal cord injury. Up to this moment there is no conclusive data about the cell types involved in the formation of heterotopic bone, although literature data suggest that all of them bear similarities to osteoprogenitor cells. Chemokines, cytokines, macrophages and macrophage-derived factors such as oncostatin M and BMP-2 have been shown to have osteoinductive abilities, suggesting a possible correlation with heterotopic bone formation. A permissive environment is also of the utmost importance.

The JAK-STAT signaling pathway is a signaling pathway involved in many biological functions. There is abundant literature that highlights the role of JAK1 and JAK2 tyrosine kinases in normal skeletal development and neural cell differentiation and proliferation. In recent years, related research has being conducted on their role in spinal cord injuries and the inflammatory process that they trigger. Besides the research of Alexander *et al.,* there is no other research that directly implicates JAK1 and JAK2 proteins in the formation of heterotopic bone in neurogenic heterotopic ossification. The role of JAK1 and JAK2 following spinal cord injuries suggests that these proteins may also be involved in neurogenic heterotopic ossification and can be potential therapeutic targets.

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REVIEW

The use of botulinum toxin in the treatment of neurogenic bladder following spinal cord injury

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ABSTRACT

Spinal cord injury patients suffer from neurogenic lower urinary tract dysfunction, associated with symptoms of urinary incontinence (UI), urgency and frequency, which may affect upper urinary tract function and has a negative impact on health-related quality of life.

Botulinum toxin is a neurotoxin derived from the bacterium Clostridium botulinum. Dykstra et al, in 1988, first injected 100 BoNT-A units into the external urethral sphincter to treat patients with spinal cord injury.

The aim of this study is to search in the literature about the effectiveness, safety and side effects of botulinum toxinin treatment of neurogenic bladder (NB) due tospinal cord injuries (SCI)

Botulinum toxin is an effective and safe option for the management of neurogenic bladder in patients who have an inadequate response to, or are intolerant of, oral medication. In SCI patients with neurogenic detrusor overactivity (NDO), botulinum toxin injection significantly decreased UI and detrusor pressure, thus increasing bladder capacity and quality of life.

KEY WORDS: botulinum toxin, neurogenic bladder, overactive detrusor, spinal cord injury

Introduction

Spinal cord injury (SCI) is a major cause of morbidity and mortality in young people, in developing countries, with 25 new cases per million. Normal bladder emptying is a voluntary action, although it is predominantly under parasympathetic control, with somatic nerves playing a lesser part. During bladder' filling phase, the urothelium release acetyl choline (Ach), nitric acid, adenosine triphosphate (ATP) and nerve growth factor (NGF) modifying the excitability of bladder afferent fibres. These afferents including small myelinated Ad and unmyelinated C nerve fibers, respond to increases in tension of the bladder wall and trigger the spinobulbospinal micturition reflex, leading to the release of Ach in efferent nerves in the detrusor muscle. This produce muscle contraction and micturition (1). In patients with traumatic subcervical spinal cord injury (SCI),

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interference with spinal pathways above lumbosacral levels releases sacral reflex activity from higher level inhibitory inputs, resulting in a variety of lower urinary tract symptoms (LUTS), generally referred to as overactive bladder. LUTS occur in most patients with SCI (1).

In traumatic SCI, during the spinal shock, there is loss of bladder control and the bladder becomes atonic. After a period of 6–8week, neuronal reorganization occurs, with the onset of spinal mediated reflex voiding and neurogenic detrusor overactivity (NDO), with or without detrusor-sphincter dyssynergia (DSD) (loss of coordination between bladder contraction and relaxation of the internal urethral sphincter during emptying phase). These changes lead to involuntary contractions of the detrusor during filling phase, interfering with the urine outflow. The symptoms of overactive bladder that are attributable to neurogenic detrusor overactivity, include urinary urgency, occurring with or without urge incontinence (UI), increase in the frequency of urination, low urine volume and nocturia (2).

This can lead to incomplete emptying of the bladder, high intravesical pressure, thus increasing the risk of infection and damage to the upper urinary tract (3). Available urodynamic tests (cysteometry, uroflowmetry, etc.) lead to diagnosis and monitor the progression of the disease over time.

Effective control of neurogenic detrusor overactivity (ND0) during SCI is a major challenge. Active treatment of these urinary conditions is essential to reduce morbidity and mortality, and to maintain health-related quality of life (HRQoL).

The primary goal of bladder management is to maintain renal function by achieving safe pressures in bladder, low rates of urinary tract infection and socially acceptable restraint (4). The loss of voluntary urination control is one of the most serious side effects of NDO and is a major cause of social isolation, as patients prefer to quit the rehabilitation process. Therefore, the management of neurogenic bladder is a priority in the rehabilitation process (5). Treatment strategies for NDO are to prevent urinary reflux and kidney damage resulting from high intravesical pressures and incontinence. The first choice treatment is anticholinergics and / or α-adrenergic antagonists, in combination with intermittent catheterization or supraventricular catheter. Anticholinergics reduce detrusor's pressure; improve bladder's capacity, improving quality of life. This therapy causes side effects in 61% of patients and effectiveness decreases over time, while increasing the dose often increases the side effects.

Botulinum toxin (BoNT) is a second choice treatment of NDO when anticholinergic drugs reduce their effectiveness (5) In 2011, BoNT-A was approved for patients with NDO after SCI by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) as botulinum toxin-A (BoNT-A).

Botulinum toxin is a neurotoxin derived from the bacterium Clostridium botulinum. Dykstra et al. in 1988, were the first to inject 100 BoNT-A units into the external urethral sphincter to treat patients with spinal cord injury.They concluded that urethral and bladder pressure decreased simultaneously.

There are seven immunologically distinct serotypes from type A to type G which have been isolated but only the A and B serotypes are commercially available. The most commonly used serotype within the lower urinary tract is BoNT-A (6).

Mechanism of action

BoNT-A appears to have a dual mechanism of action on both the motor and sensory pathways responsible for NDO, blocking the release of acetylcholine in neuromuscular junction. This inhibits parasympathetic signaling to the bladder, reducing involuntary detrusor contractions, reducing the ability of the detrusor muscle to contract. This reduction in contractions reduces NDO symptoms (6). The inhibition is temporary, but generally it lasts for 6 to 9 months. Muscle contraction will return after the effect of medication, as neurons regain the ability to release neurotransmitters. After the injection with the BoNT-A, the average number of daily incontinence episodes decreased steadily, the urinary urine volume almost doubled after each treatment and total I-QOL scores were increased following botulinum toxin-A 200U injection, as demonstrated in two randomized, multicenter, multinational Phase III studies (7). Both motor and sensory effects

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are reversible, but regeneration of sensory receptors appears to take longer and it is the sensory effects which determine the duration of action of BoNT-A (6). The suggested doses are 200U to 300U, since no improvement was observed with higher doses.

The effectiveness of BoNT-A is monitored by results of the urodynamic parameters (compliance of the detrusor, bladder capacity, maximum detrusor pressure) and from the opinion of the patients for their well-being. The effectiveness of a BoNT-A injection lasts, on average, 9 months, although patients experience beneficial effects for up to 12 months or more during the first 4 years of cyclic therapy. Overtime, the effectiveness of BoNT-A decreases until complete loss of its therapeutic effects. On average, 12-14 years after the first injection, 60% of patients still experience beneficial effects, while 40% of them have stopped treatment (5).

Side effects and contraindications

The most commonly observed side effects after toxin injections are urinary tract infections (UTI), the increased urinary retention andrarely - general muscle strength that can last 1-2 months.Side effects are temporaryand can be treated with antibiotics and clean intermittent catheterization (CIC). BoNT A injection into the detrusor is contraindicated for use in patients with UTI or bladder plaster. It is also contraindicated for patients who do not use CIC, if they have urinary retention at the time of injection and for those who are unable or unwilling to start CIC if required after treatment.

The *safety and efficacy* of BoNT A have not been established inpatients with NDO and incontinence who are aged 18 years and the drug is not recommended for use in this age group.

Antibody Formation NAbs

Botulinum neurotoxins have the potential to elicit immune responses in humans, including the development of neutralizing antibodies (NAbs).The risk of developing NAbs is low. If and when it occurs, it can reduce the effectiveness of treatment. Because Nab formation may be more likely with frequent injections and at higher doses, the use of BoNT-A at the lowest effective dose and for the longest clinically indicated period is recommended (1).

This treatment is minimally invasive and causes a significant reduction in morbidity as well as the costs associated with essential drugs (7).

In SCI patients, a serious and threatening condition is autonomic dysreflexia. In a SCI animal model, BoNT-A intravesical injection significantly decreases NGF levels in the bladder and in the dorsal root ganglion of the T4 root. Several studies report that BoNT-A block autonomic dysreflexia, suggesting that NGF interferes with the etiology of autonomic dysreflexia and that BoNT-A therapy, might control this condition (1).

The aim of this study was to assess effectiveness, safety and side effects of botulinum toxinin treatment of neurogenic bladder (NB) due to spinal cord injuries (SCI). A literature search was performed on published articles mainly in PubMed database, using the following key words: botulinum toxin, neurogenic bladder, overactive detrusor, spinal cord injury. A total of 264 articles were initially identified for use in this study, 258 in PubMed and 6 from other sources. Of these, 35 were excluded as duplicates. Of the remaining 229 articles, 81 were excluded by reading titles and abstracts. Of the 148 remaining full- text articles 124 articles were excluded due to antiquity (<2005). Eventually, 24 full -text articles were included in this study.

Discussion

The first-line pharmacotherapeutic treatment for neurogenic bladder, are muscarinic receptor antagonists. However, patients may have a suboptimal response or find that antimuscarinic therapy is limited by associated AEs, therefore, there is a need for a new treatment that is effective, well-tolerated, with a distinct mechanism of action. The BoNT-A injection into the detrusor muscle has been demonstrated in neurogenic bladder. Also BoNT-A may be a useful treatment to augment existing NDO treatments or other invasive surgical options.

The last two decades, treatment of lower urinary tract conditions using BoNT-A has rapidly expanded. In the literature, there has been a large number of studies investigating the effective and safe use of the BoNT as well as the most effective dose with the

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fewest side effects. So far, BoNT-A is a well-established therapy in the management of neurogenic detrusor overactivity (NDO) and is recommended by the majority of international bodies and guidelines as a second-line treatment for NDO in patients who have symptoms refractory to antimuscarinics or β3 adrenoceptor agonists (6). Cruz et al (8) compared BoNT-A with placebo in terms of efficacy and safety in patients with NDO secondary to SCI, in two double-blind, placebo-controlled, randomized DIGNITY trials. Patients with NDO who experienced UI episodes and were not sufficiently managed with anticholinergic agent were randomized to receive either BoNT-A 200U, 300U or placebo. Patients had to be using clean intermittent catheterization (CIC) or be able and willing to do so. At week 6, in both studies, BoNT-A 200U significantly reduced UI episodes / week and improved MCC and Pdetmax IDC compared with placebo (P<0.001). Also patients without an involuntary detrusor contraction were notably more in the BoNT-A group compared with placebo, indicating that BoNT-A decreases a major risk factor (duration of the involuntary detrusorcontraction) for upper urinary tract impairment. Duration of positive effect for BoNT-A group was 38.4 weeks, with meaningful changes in I-QOL scores. In this study the most common reported adverse events were urinary tract infection (UTI) and urinary retention, while in one third of BoNT-A patients, CIC was initiated due to urinary retention compared with almost none in placebo. Authors mention that the use of BoNT-A in patients with high cervical lesions above T1 should be careful, due to the risk of developing muscular weakness in the respiratory muscles. The positive effects after BoNT-A treatment were independent of anticholinergic use. However, more studies are required to investigate additional benefit from combination therapy. After repeated injections of BoNT-A 200U the UI episodes per week were consistently reduced over five cycles of treatment and also there were statistically significant improvements from baseline in all I-QOL.

X.-T. G et al. (4) evaluated the effects of Botulinum Toxin A injection into the detrusor muscle, measuring voiding parameters in SCI patients with detrusor overactivity and urinary incontinence who were refractory to oral medications. They concluded that the use of botulinum toxin in the treatment of neurogenic detrusor overactivity in patients with SCI is safe, valuable and promising option especially to those who resisted to anticholinergic medications. They noted that BoNT-A 300 IU into the detrusor, showed significant effects on the episodes of incontinence per day, maximal voiding volume, and urodynamic parameters (cystometric capacity and maximal detrusor pressure). They noted remarkable reduction in incontinence episodes of approximately 50% from base line at 6 and 24 weeks after treatment. There was no increase in AE rates over repeated treatments, suggesting that BoNT-treated patients were completely dry after 24 weeks post-injection. The urodynamic study showed signifying decrease of maximum detrusor pressure, increase of the mean cystometric bladder capacity after injection at 2 and 24 weeks (P<0.05). Quality of life and patient' satisfaction were remarkably improved due to decrease of leakage, and number of incontinence.

Kennelly et al. (7), in a long-term extension study investigating the efficacy and safety of BoNT-A, demonstrated that treatment with BoNT-A 200U is effective and well tolerated through 4 years. They also confirmed that there are non-clinically relevant differences in the treatment response between BoNT-A 200 and 300U dose groups. Repeated treatment with BoNT-A led to excessive reduction in the number of daily UI episodes. After 4 years of observation, they noted >50% decrease in UI episodes, while 43–56% of patients achieved complete continence, markedly higher than in other treatments for NDO. Following each treatment with BoNT-A, it was noted consistent increase of volume/void. In addition, the remarkable improvements in urinary symptoms, after BoNT-A treatment, kept up with meaningful improvements in QOL, suggesting that BoNT-A could maximize treatment success. The therapeutic effect of BoNT-A across all patients was 9 months. In this study the reported AEs were UTIs, while the rate of treated UTIs was rather reduced. Observation of long-term treatment with BoNT-A noted that there was no increase in AEs rates, suggesting that BoNT-A did not have a cumulative action or toxic duration. After the first BoNT-A treat-

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ment, the incidence of CIC was greatly reduced during following treatments. These results suggested that if patients did not initiate CIC during their first BoNT-A treatment, they would rather not need to initiate CIC at all. In this extension study the rate of antibody formation was low in patients, and half of the antibody positive patients continued to experience clinical benefit. The authors concluded that there was clinically serious improvement in urinary symptoms and QOL following BoNT-A treatment in patients with UI, due to NDO, who are inadequately managed by >1 anticholinergic medication ,during the 4-year study, with no new safety signals.

Zhang et.al (9), in a review study with eight selected studies (n=1879 participants), noted that the use of BoNT-A was related to urinary tract infection (UTI) in both BoNT-A 200U and 300U groups, significantly higher than the placebo. There was significant reduction of the frequency of urinary incontinence episodes in BoNT-A group compared to placebo. Authors noticed that the maximum cystometric capacity (MCC) was incised and maximum detrusor pressure (MDP) was decreased than the placebo, with no statistical differences between BoNT-A 200U and 300U doses in UTI, MCC and MDP. Evaluation of the impact of BoNT-A 200U and 300U on QOL showed significant improvement in the mean change from baseline, which was superior to the effect of placebo ($p<0.001$), at weeks 6 and 12. They concluded that BoNT-A provided clinical and urodynamic benefit for populations with NDO but did not find clear dose differences (200 VS 300 U).

Sheng-Mou Hsiao et al (39) concluded that the therapeutic effects of BoNT-A can last till 6 months after treatment, while female gender, low overactive bladder symptoms score (OABSS) and the presence of OAB-wet were associated with better therapeutic efficacy.

Sheng-Fu Chen et al (11), in a small study, attempted to investigate the therapeutic effects on urothelial dysfunction after repeated detrusor injections of BoNT-A in SCI patients with neurogenic detrusor overactivity (NDO). The patients received 300 U BoNT-A injection into the detrusor every six months. The urothelium was assessed by cystoscopic biopsy. The authors determined the adhesive and tight junction protein levels, at baseline and six months after each BoNT-A treatment. After repeated BoNT-A injections a significant increase in cystometric bladder capacity (CBC) and post-void residual (PVR) volume, and a significant decrease in detrusor pressure at Qmax (Pdet.Qmax) were shown. They noticed that the urothelial barrier function recovered by improving adhesive and tight junction protein levels, providing evidence that repeated BoNT-A injections can have a sustained therapeutic effect on NDO in SCI patients.

Jean-Jacques Wyndaele (2) mentioned that treatment with BoNT-A seems to be safe and effective, with positive effects on many urodynamic and clinical parameters, lasting for 6 to 16 months. However, no additional benefit results from the combination of BoNT-A with antimuscarinics was noted, while the repeated injections of BoNT-A seemed to produce similar effects to those of the previous injection. The most important adverse events mentioned were the increased PVR in patients who could void a higher incidence of UTI and rarely a loss of general muscular power that could last for 1–2 months.

Soler et.al (12) conducted a study to determine outcome predictors for urethral injection of 100 U BoNT-A to treat detrusor sphincter dyssynergia (DSD) in patients with spinal cord injury. They concluded that strong predictors of excellent outcome were the detrusor contractions and normal bladder neck activity.

Moore et al. (13) evaluated the change in UI episodes per week, and secondary outcomes included urodynamics (UDS) findings and Incontinence Quality of Life (I-QOL) score in patients with NDO who received BoNT-A 200 U, 300 U, or placebo. It was recorded statistically significant decrease in UI episodes per week in the 200 U and 300 U groups, when compared to placebo. In all patients, they noted significant increases in their I-QOL scores compared to placebo. Six weeks after injection, repeat UDS studies were performed. Patients treated with 200 U and 300 U showed increased maximum cystometric capacity (MCC) and maximum detrusor pressure during first IDC, compared to placebo. Authors reported that the most frequent AEs were UTI across all patients, which was defined by

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positive urine culture. In SCI patients, the reported incidence of UTI was similar between BoNT-A and placebo (44.8% and 49.5%, respectively). Evaluation of long-term efficacy of BoNT-A injections for NDO patients demonstrated sustained improvements in UI episodes per week and I-QOL score. The number of new patients initiating CIC decreased dramatically with each treatment; those who did not require CIC after three treatments ever went on CIC. Reported AEs and AE rates were similar. With 200 U dosing, the median duration of treatment effect was nine months.

Detrusor Sphincter Dyssynergia (DSD) can lead to incomplete emptying, thus increasing the risks of UTI and upper urinary tract damage. Authors referred to small studies in which demonstrated the efficacy of 100 U BoNT-A injection into the external sphincter for treatment of DSD. Meta-analysis of these studies in patients with SCI noted a reduction of PVR after treatment with BoNT-A lasting up to six months, as well as a reduction in UTIs and CIC in some series. AEs described in these studies have been minimal.

Cheng et al (14) evaluated the efficacy of different doses of BoNT-A in patients with NDO, performing a meta-analysis with six randomized controlled trials (RCTs) to assess the AEs associated with BoNT-A use. The study compared three groups (BoNT-A 300U, BoNT-A 200U group and the placebo group) with the reported data for the mean changing from baseline of UI episodes per week (at 6 weeks). There were significant decreases in UI episodes in the BoNT-A 200U group (P<0.00001) and the BoNT-A 300U group (P<0.00001). Compared to the placebo group, there was no significant heterogeneity in either BoNT-A group. Interestingly, there were no significant differences between the BoNT-A -treated groups in the number of weekly UI episodes (P=0.95). This result suggested that BoNT-A has significant beneficial effects in UI episodes compared to a placebo. This meta-analysis showed improvements in the urodynamic parameters. Treatment with BoNT-A (200U and 300U) compared to the placebo was significantly superior for increasing the maximum cystometric capacity (MCC) and reducing the maximum detrusor pressure (MDP). However there was no significant difference between the two BoNT-A-treated groups (P=0.56). In this study, all reported Adverse Events **(**AEs) including rate of UTIs, urinary retention, hematuria, and muscle weakness were either transient or easily manageable and dose-related, in patients not using CIC. The results reported the main AEs as UTIs (P<0.00001), urinary retention (P<0.00001), hematuria (P=0.05), and muscle weakness (P=0.004). In conclusion, this meta-analysis demonstrated that a statistically significant improvement in the frequency of incontinence and urodynamic parameters was reported in the BoNT-A 200U and 300U groups versus the placebo. Also in almost all patient QoLs was significantly improved in the BoNT-A -treated groups following treatment, and changes in the urodynamic parameters were accompanied by improvements in patient symptoms.

Duthie JB et al (15) support the efficacy of botulinum toxin in the treatment of OAB. There are limited data about the long-term safety, optimal dose and best injection technique, despite some studies trying to explore these issues with higher doses of botulinum toxin. There were various thresholds for commencing CIC. There is some suggestion from the data that lower doses may offer comparable efficacy with fewer adverse events, albeit for a shorter duration than higher doses. The effect of BoNT-A treatment may last from three to twelve months, while the botulinum toxin type B treatment seems to be limited less than ten weeks.

Yuan et al (16) performed a systematic review with 6 randomized double-blind, placebo-controlled trials, involving 871 patients, to assess the efficacy and safety of BoNT-A treatment in neurogenic detrusor overactivity. The results suggested that BoNT-A significantly reduced the daily frequency of UI and MDP during first involuntary detrusor contraction, and improved MCC in patients with UI due to NDO. Also, the BoNT-A was regularly associated with complications localized primarily to the urinary tract. Higher rates of increased PVR may be found.

Hui-Yun Gu et al (17), in their systematic review and meta-analysis including 11 studies comparing doses of 200U and 300U vs placebo at 2 ,6 12 and

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36 weeks after treatment, concluded that BTX-A 300U and 200U significantly improved symptoms of NDO (UI episodes per week, MCC, and I-QOL), compared with placebo. Jianshu Ni et al (18), in a systematic review and meta-analysis, demonstrated that sustained improvements were noted in patients with NDO after repeat BoNT-A injections. They analyzed eighteen studies, involving 1533 patients with SCI and MS after the first and last injections. Only minor non-significant changes in MCC, MDP, RV, and BC (bladder compliance) were noted. After the first and last injection, in the group that received ≤4 injections, stable improvements in QOL was noted, whereas in the group that received ≥5 injections, a moderate decreased of QOL ($0.5 < SMD < 0.8$) was reported after the last injection. In this study, for patients who received repeat injections of BoNT-A300 U, the improvement in QOL was stable until the fifth injection, while significant decrease in QOL was noted after the last two injections. In the same study, dose of BoNT-A 200 U improves QOL until the ninth injection. These results may be caused by the difference in the treatment dose. No significant change in the intervals between repeat BoNT-A injections was observed. In all studies, sustain improvement in UI was noted by the repeat BoNT-A injections and results were consistent with the outcomes of urodynamic variable. The most frequently reported AEs were urinary tract infection, urinary retention and hematuria. The rate of AEs was stable and low. This analysis confirms the efficacy and safety of three to four injections, suggesting that BTX-A does not have cumulative dose or duration toxicity.

The study of Aaron Kaviani et al (19), through 2 double-blind, placebo-controlled, phase III studies, compared the response to BoNT-A with response to placebo in patients with NDO due to SCI or MS. The results showed that BoNT-A injections effectively decreased UI, improved UDS parameters and increased QOL. So, there is strong evidence that intradetrusor BoNT-A injection, in treatment of refractory NDO in SCI patients, is associated with significantly improved UDS performance and achievement of patients' goal.The mostcommon adverse events reported are urinary tractinfections (UTI), increased postvoid residual and the need for de novo CIC, especially in patients who do not already perform CIC. They also referred that the potential effect on autonomic dysreflexia is a clinically important consideration of the use of BTX-A in SCI patients. Animal and human studies have shown that intradetrusor injections of BTX-A decrease the severity and frequency of bladder-related incidents of autonomicdysreflexia (AD).

Young Sam Cho et al (20), reported a significant improvement of urodynamic parameters including increase of the maximum cystometric capacity (MCC), decrease of the maximum detrusor pressure (MDP) and incontinence episodes after BoNT-A treatment, in SCI patients with NOB. The improvement was noted after the first injection and then remained constant after 4-5 repeated injections at 2 weeks and continued throughout the 6-month period. Moreover, at 6 months, a significant improvement in QoL was observed. In order to minimize the need for clean intermittent catheterization (CIC), due to urinary retention caused by BoNT-A, a 200U dose rather than 300U, was used.This study documented a reduced need for anticholinergic medications after the injection, while a beneficial effect on AD was noted after BoNT-A injection into the bladder wall. After BoNT-A, the most common reported adverse effects (AE) were the UTIs (pyelonephritis, orchitis, prostatitis) and the increase of postvoid residual urine (PVR).

In order to evaluate the efficacy and safety of BTX-A, according to injection site in NOB, Jung Ki Jo et al (21) conducted this meta-analysis.The use of different BoNT/A injection sites to treat OAB leads to different outcomes. Between intradetrusor and suburothelial injection sites, there were no differences in efficacy or safety regarding the incidence of vesicoureteral reflux, hematuria, general weakness, bladder discomfort, large post-void residual and urinary tract infection.Improvement in patient symptoms(higher complete dryness rate and lower frequency of incontinence episodes) was noted in Trigone-including injection. Trigone-including injection also provides patients with higher volume at the first void following treatment, with lower detrusor pressure and without an increase in adverse ef-

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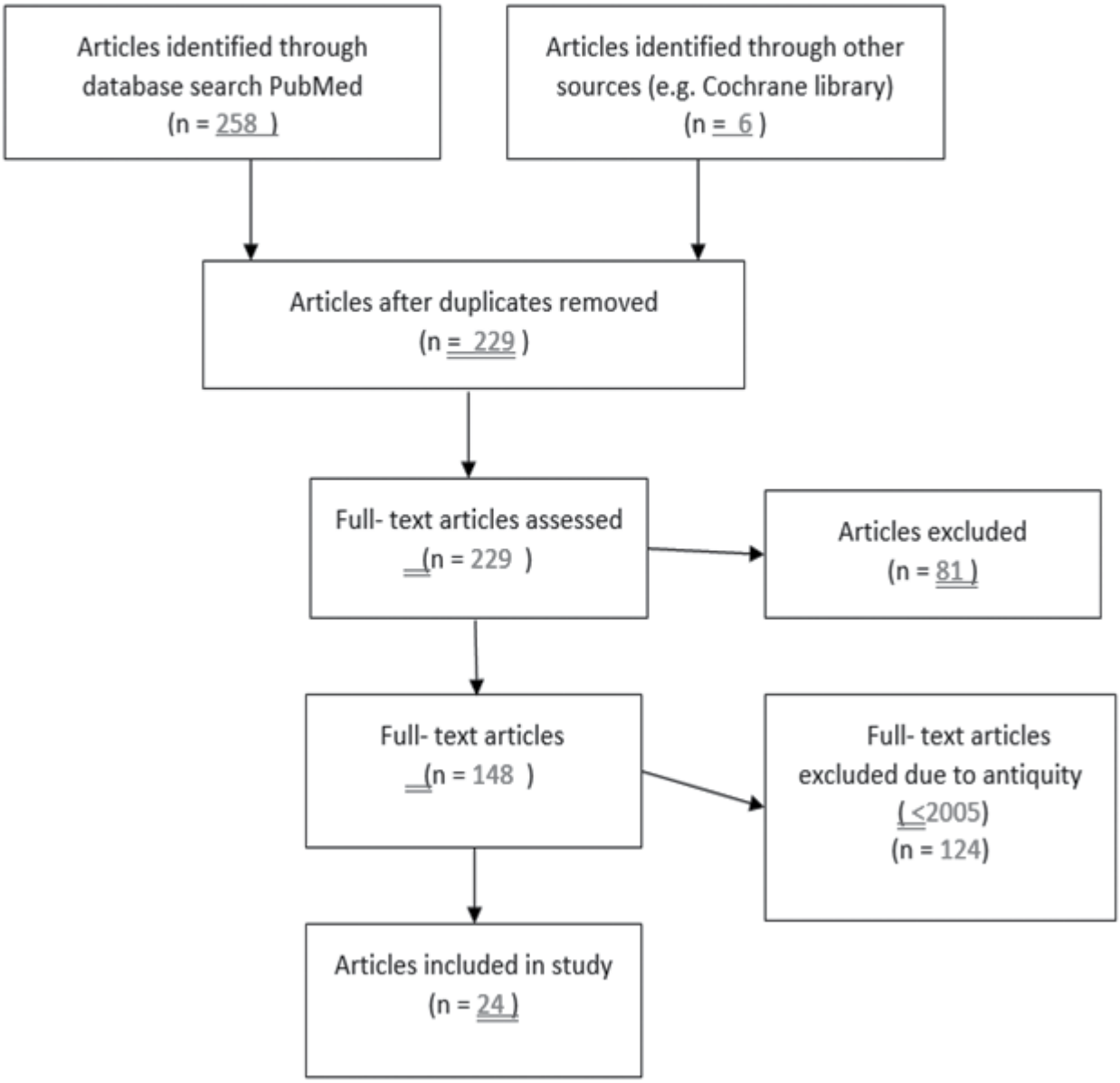
Flowchart of the study selection process



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fects. In contrast, according to depth of injection, no difference in efficacy or safety findings were shown.

David Eldred-Evans et al (6), in their review for the use BTX-A in voiding dysfunction due to detrusor sphincter dyssynergia (DSD), noticed improvements in QMax, maximum urethral closure pressure, frequency of voiding and QoL. Also, the meta-analysis of SCI patients found a mean post-void residual (PVR) decrease for up to 6 months. Nevertheless, they noted that the current evidence for BoNT-A in DSD is of limited quality due to the small number of participants in level 1 trials and the risk of bias from observational studies. The authors also mentioned that a surgical sphincterotomy may provide greater efficacy and longer duration effect.

Jeremy B. Myers et al (22) in a multicenter, prospective, observational study in SCI patients performing CIC, found that patients who underwent cystoplasty had better scores on quality of life scales and NBSS (Neurogenic Bladder Symptom Score), than those who underwent catheterization with or without the use of toxin. They also observed that there no significant improvements in urodynamic parameters and quality of life as a result of the use of toxin, as observed in other studies.

Guang-Ping Li et al (23,) in a systematic review and meta-analysis of 17 studies involving 1,455 patients, compared with placebo and baseline and noted that BoNT-A was effective in increasing maximum cystometric capacity (MCC), volume at first involuntary detrusor contraction (Pdet), compliance, the number of patients with complete dryness (CD) and decreasing detrusor pressure, the number of patients with no involuntary detrusor contractions, the maximum flow rate, the incidence of detrusor overactivity and the number of urinary incontinence (UI) episodes. There were no statistically significant differences between doses of 200 U and 300 U or between injections into the detrusor and submucosa. In addition, comparing the injection locations (sparing the trigone and excluding the trigone) both methods increased the number of patients with CD, improved IQoLdecreased UI episodes, and Pdet. However, sparing the trigone was considered preferable. The most common referred AEs were symptomatic urinary tract infection. They concluded that BoNT-A is effective and safe in treating NDO after SCI.

Guoqing Chen et al (24), conducting a small study in patients with neurogenic detrusor overactivity, underwent BTX-A injection into the urethral sphincter. After treatment, they report that the maximum urinary flow rate was increased, while residual urine, maximum urethral pressure and detrusor leak point pressure were decreased. Patients still did not completely detach from CIC, but they can partially urinate autonomously, and the frequency of CIC was reduced improving the quality of life. The effect of BTX-A lasts for only three to 4 months and repeated injections were required.

In conclusion, BTX-A injection is a safe and valuable therapy, in the treatment of neurogenic bladder due to SCI. Significant improvement in incontinence severity, urodynamic parameters and QoL measures was observed, in most patients who received repeated BTX-A, without any significant difference between the 200-Uand 300-U dose.

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CASE REPORT
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Necrotising fasciitis of the lower extremity following streptococcal pharyngitis

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ABSTRACT

Necrotising fasciitis is a grave infectious process affecting the fascia, the overlying soft tissues, and, occasionally, the underlying muscle. Various bacteria can be the cause of this aggressive and fast progressing disease. Skin lacerations or surgical wounds are the portal of entry in most patients; however, hematogenous spread of the microorganism can occasionally initiate the process. Streptococcal pharyngitis (group A β hemolytic streptococcus – GAS) followed by necrotizing fasciitis of the lower limb is a very rare finding with only a few case reports found in the literature. Two such cases of necrotising fasciitis of the left lower limb with similar features treated by the same surgeon at two different hospitals in two different countries are presented. The outcome was favorable in both patients. The diagnostics and appropriate mode of treatment are reviewed. The importance of early surgical intervention is stressed, as it can save lives.

KEY WORDS: Necrotising fasciitis, myositis, lower limb, surgery, urgency, pharyngitis, streptococcus, gangrene.

Introduction

In the 16th century, Ambroise Paré described a gangrene-like condition that resembled today's "flesh-eating disease" (1). A similar soft-tissue infection was described during the American Civil War (2). In 1952, Wilson proposed the term "necrotising fasciitis" to replace terms like gangrenous erysipelas, hospital gangrene, acute cutaneous cellulitis, streptococcal gangrene, Meleney cellulitis, and others (3).

Necrotising fasciitis (NF) is a subset of the aggressive skin and soft tissue infections which cause necrosis of the muscle fascia and subcutaneous tissue. Even today, the disease has a high mortality rate (1, 2). This infection typically travels along the poorly vascularized fascial plane leaving the overlying tissues initially unaffected, potentially delaying diagnosis and surgical intervention (4). The infectious process can rapidly spread to peri-fascial planes, causing a secondary infection of the overlying skin and underlying soft tissue and muscle (necrotising fasciomyositis). The estimated annual incidence in the United States in 2018 was 10.3 (National Inpatient Sample) and 8.7 (Watson Health Dataset) per

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100,000 persons, respectively (5). The incidence has been demonstrated to be increasing, as in 2009 it was reported 4.3 infections per 100,000 (6). NF places significant demand upon hospital and medical resources. An Australian study reported that the mean hospital length of stay for survivors of NF was 36 days, and the average cost per patient during their stay was AUS $ 64,517 (7).

NF can affect any part of the body; the extremities, however, the perineum and the truncal areas are the most commonly involved. Most patients present with signs of inflammation such as erythema, swelling and pain at the affected site (6, 8, 9, 10). However, these symptoms may be non-specific at first, which often causes the diagnosis to be missed. Severe pain disproportionate to local findings, and occasionally associated with systematic toxicity, should raise the suspicion of necrotising fasciitis (6, 11, 12). As the infection progresses, the skin becomes increasingly erythematous and tense with indistinct margins. It may change color from red-purple to a dusky blue before progression to necrosis and formation of bullae (blistering) which eventually become hemorrhagic. Blistering is due to ischemia- induced necrolysis, as the invading organisms cause progressive thrombosis of vessels that penetrate the fascia to supply skin (13). Crepitus may be palpated over the affected area due to gas produced by aerobic and anaerobic bacteria. The skin lesions may turn black and form a necrotic crust, with fascial tissue and brown-grayish secretions underneath the crust (6). Symptoms may develop over a period of hours to several days, and presentations vary (11). Patients presenting at an advanced stage may show signs of systemic shock and sepsis. They pose extra diagnostic difficulties since they may be confused, agitated or have a reduced level of consciousness.

The most common portals of entry are sites of prior surgery or trauma, contusions and skin lesions (1, 6, 12). Malignancies and other conditions can play a role as predisposing factors. NF, however, can also occur idiopathically, with no previous history of surgery, trauma, skin lesions etc. Pharyngitis and early hematogenous spread of the infection is a very rare occurrence. Our aim is to present two cases of otherwise healthy patients, who shortly after streptococcal pharyngitis developed NF of the left lower extremity. The history, clinical course, treatment and follow-up of this disease are reviewed and the importance of early diagnosis and surgical intervention is discussed.

Case One

A 45-year-old previously healthy male patient (A. M.) was referred by his general practitioner (GP) to the Accident & Emergency Department (A&E) at the University College Hospital, London (UCLH NHS Trust) because of pain in his left hip and thigh. Four days earlier he had visited his GP because of a sore throat, for which amoxicillin (capsules 500mgr, 3xdaily) was prescribed. Two days later, the patient returned to his GP complaining of pain in the left hip/thigh area. He was a denizen of the gym; therefore, some kind of muscle or hip injury was suspected and ibuprofen (tablets 400mgr, 3-4xdaily) was prescribed with little effect. Thence, he was referred to the A&E Dept. of the UCH. At arrival, the patient was pyrexial (38.3 C), and complained of severe pain in and around his left hip and thigh. Orthopedic physical examination revealed erythema and tenderness of the skin over the left thigh. No other abnormal physical signs were detected. Plain x-rays of the left femur, left hip joint and pelvis were within normal limits. A CT-scan showed non-specific edema of the soft tissues of the left thigh (skin, subcuta-neous fat and muscles). Laboratory values were: AP 100/70, pulse 90/min, PA 22/min, Hb 11.5 gr/dL, leucos 16,300/ml, CRP 18.3, Na+ 132 mmol/L, creatinine 1.6 mg/dL, glucose 106 mg/dL. A throat swab was taken which showed the presence of group A β-hemolytic streptococci. The consultant orthopedic surgeon (B.C) was highly suspicious of a necrotic infection and together with the consultant P/R surgeon on call (Ch. I) carried out a "finger-test" (small skin incision under local anesthesia over the area of maximal suspicion, blunt dissection down to the fascia and examination of the fascia with the finger. A finger along the fascial planes that easily dissects the overlying tissue without resistance was a positive test. Having established a differential diagnosis of necrotising fasciitis, the patient was taken to the operating theatre, where under general anesthe-

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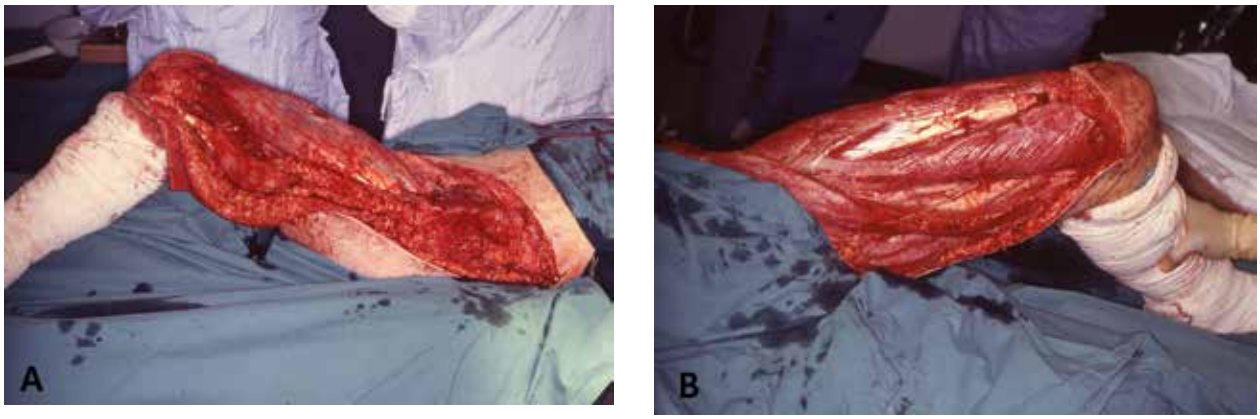

Fig.1. *Patient one after surgical debridement of left thigh/trunk area. A. Lateral aspect. B. Medial aspect.*

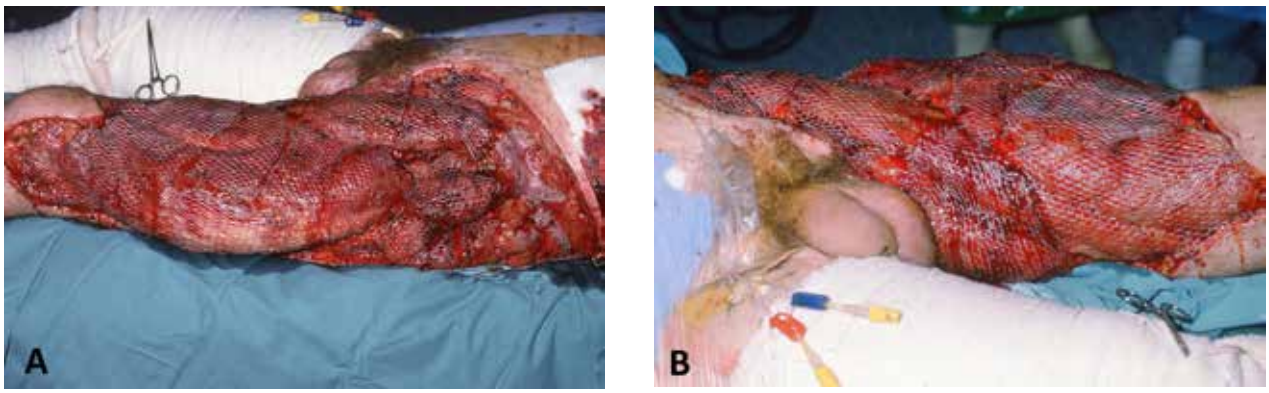

Fig.2. *Patient one after cover of thigh/trunk defect with meshed skin grafts. A. Lateral aspect. B. Median aspect.*

sia the suspicious skin, underlying fat and necrotic fascia of the left thigh and part of the left trunk were surgically debrided. The left rectus femoris muscle looked clinically necrotic (blackish, brittle) and was also debrided (Fig. 1). The patient was transferred to ICU and the triple antibiotic regimen (initiated in theatre) was continued. Postoperatively, the patient's condition improved dramatically. Further surgical exploration was conducted 24h later and further debridement of peripheral soft tissues and muscle parts was performed. Another two surgical debridements had to follow till all necrotic tissue was removed and the patient's condition stabilized. Seven days later he was returned to the ward. Blood cultures showed the presence of group A β-hemolytic streptococcus. After several days (d 14) and two consecutive negative wound swabs, the left extremity/trunk defect was covered with meshed split thickness skin grafts harvested from the right thigh. There was a 100% take of the skin grafts (Fig. 2) and the patient was discharged from hospital in a good condition on day 23. He received intensive kinesio/physiotherapy and could return to normal physical activities three months after discharge. Follow-up at 8 months showed a normally functioning and aesthetically acceptable left lower limb (Fig. 3). The patient has been healthy and well, and free of symptoms for five years.

Case Two

A 46-year-old white male patient was admitted to the department of internal medicine at IASO General Hospital, Athens (S. G) with fever, weakness, general malaise and vertigo. Five days previously, while skiing in Switzerland, he felt unwell (sore throat, pyrexial, general malaise), and was prescribed antibiotics (amoxicillin tabs. 500mgr, 3xdaily) by the local general practitioner. Three days later

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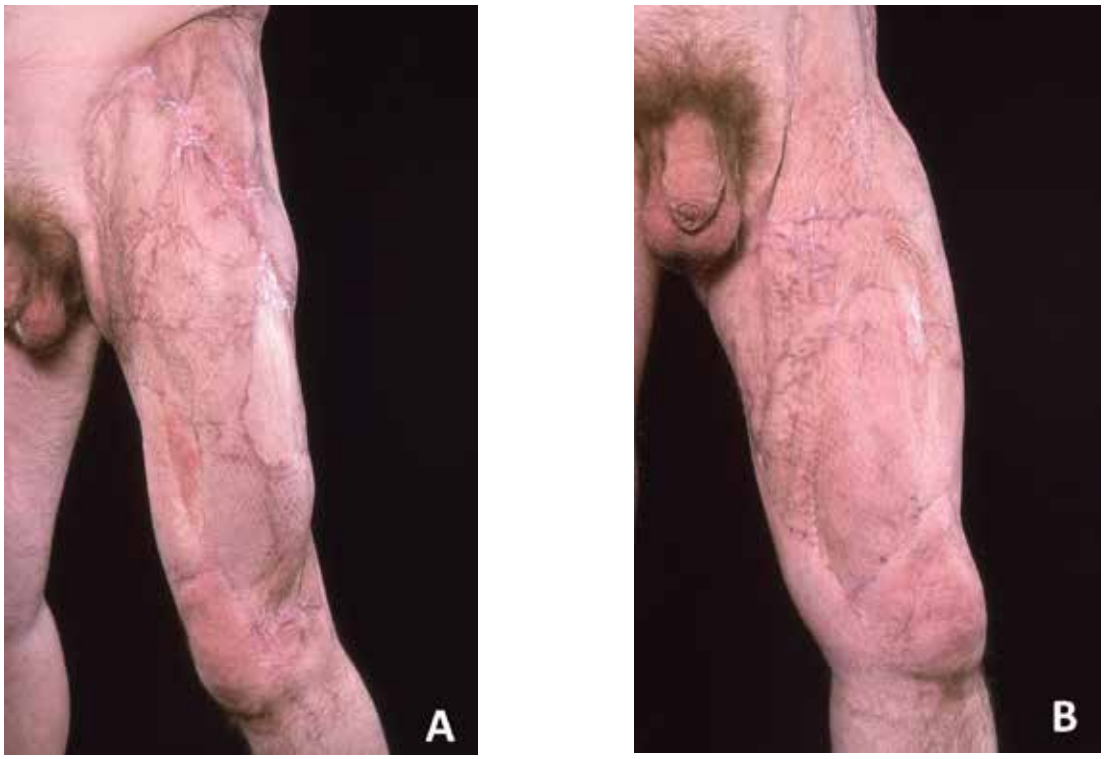

Fig.3. *Patient one eight months postoperatively. A. Lateral aspect. B. Medial aspect.*

his situation did not improve and he returned to his homeland (Athens, Greece). Upon telephonic consultation with his internist, hospital admission was suggested. From the medical history, tonsillectomy and hemorrhoidectomy were reported. On physical examination, the patient presented septic. His pharynx was erythematous and the skin of the left thigh showed signs of cellulitis (Fig. 4). Temperature was 37.9C, pulse 100/min, arterial pressure 70/50 mmHg, respiration 20/min, Hb 15.9 g/dL, Ht 45.3 %, leucocytes 17,330 (neutrophils 96%), SR 92, CRP 57.8 mg/dL, platelets 303,000, urea (BUN) 52 mg/dL, creatinine 1.3 mg/dL, Na+ 139mmol/L, K+ 4mmol/L, glucose 128mg/dL, D Dimers 2,688 ng/mL, CPK 527 IU/L (LRINEC score 5). A pharyngeal swab was taken for culture, which grew group A β-hemolytic streptococcus. The patient was resuscitated and put on IV antibiotics (clindamycin/Dalacin 600mg 3xdaily, moxifloxacin/Avelox 400mg once daily, amikacin/Briklin 1gr once daily). The following day his condition deteriorated; Hb 11.2 g/dL, Ht 32.8%, leucocytes 28,120 (neutrophils 94%), CRP 39.1 mg/dL, platelets 219,000, BUN 70 mg/dL, creatinine 2.2 mg/dL, Na+ 137mmol/L, K+ 4.1mmol/L, glucose 150 mg/dL, CPK 448 IU/L (LRINEC score 9). The antibiotic regimen was adapted (daptomycin/Cubicin 700mg once daily, clindamycin/Dalacin 600mg 3xdaily, doripenem/Doribax 500mg 3xdaily). An ultrasound of the left thigh showed oedema of the skin and adipose tissue, as well as increased vascularity of the anterior surface of the thigh, suggestive for cellulitis. The sartorius muscle and to a lesser extent the vastus medialis were edematous. There was no gas or fluid collection. The left inguinal lymph nodes were somewhat enlarged. The MRI of the left thigh showed extensive oedema of the skin and fat, a thickened deep fascia as well as thickening of the sartorius muscle, and to a lesser extent of the vastus medialis. There was a limited fluid collection around the sartorius muscle. At this point, surgical consultation (Ch. I) was sought and as the clinical picture was suggestive of necrotising fasciitis, a "finger-test" (and frozen sections) was suggested. It is worth noting that the infectious disease specialist wrote: "Even if the clinical and radiological picture is against a possi-

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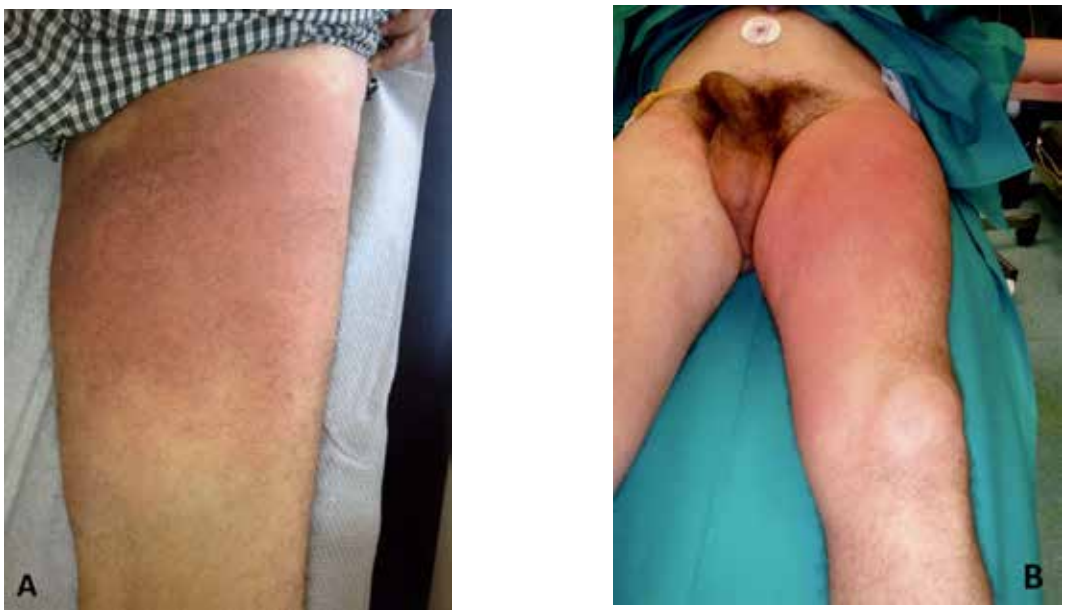

Fig.4. *Left thigh of patient two. A. On day one. B. On day two. The erythema is markedly more extensive.*

ble necrotising fasciitis, I agree with the minimally invasive test (finger-test by P/R surgeon) in order to exclude NF". The evening of day 2, under local anesthesia a small skin incision on the anterior surface of the patient's left thigh was performed with immediate pus flow through the wound (Fig. 5). The "finger-test" was positive. A small fat/fascia tissue specimen was resected and sent for frozen section. According to the pathology report, the adipose/connective tissue showed extensive necrotic inflammation, which extended to the fibrocollagenous septa, around the vessels and into the fatty tissue. There were sites of liponecrosis (Fig. 6). Furthermore, congested vessels and sites of recent hemorrhage could be identified (Fig. 6). The histologic picture along with the clinical picture was highly suggestive of necrotising fasciitis. The patient was taken to the operating theatre, where under general anesthesia a wide surgical debridement of the skin, adipose tissue and fascia of the left thigh was performed. Necrotic parts of the left sartorius muscle and the vastus medialis were also excised (Fig. 7). Postoperative improvement was spectacular. Fluid resuscitation and IV antibiotics continued on ICU. Histological examination of the paraffin sections confirmed the frozen section diagnosis of necrotising fasciitis showing furthermore acute inflammation, extensive necrosis and hemosiderin deposits of the fascia lata. Blood cultures showed the presence of group A hemolytic streptococcus. Daily inspection of the wound under sedation showed no further extension of the necrotic process. After two negative wound swabs, split thickness skin grafts from the right thigh were used to cover the defect (day 12). Skin graft take was 100% (day 19) (Fig. 8). There were no further sequelae and the patient was discharged from hospital on day 22 in a good condition. Dressing changes and cauterization of hypertrophic granulation tissue between the skin grafts (Fig. 8) were performed on an outpatient basis. Intensive physio/kinesiotherapy helped the patient regain functionality and muscular strength of the lower limb (and avoided lymphedema of the lower leg and foot). He returned to his normal sports activities (football-amateur) one year later (Fig. 9). He has been followed for 7 years without pathological signs or need for readmission.

Discussion

Necrotising fasciitis (NF) is a rapidly progressive, destructive soft tissue infection with high mortality. There are four types of NF: Type I is polymicrobial with at least one anaerobic species with one or more facultative anaerobic streptococci and members of

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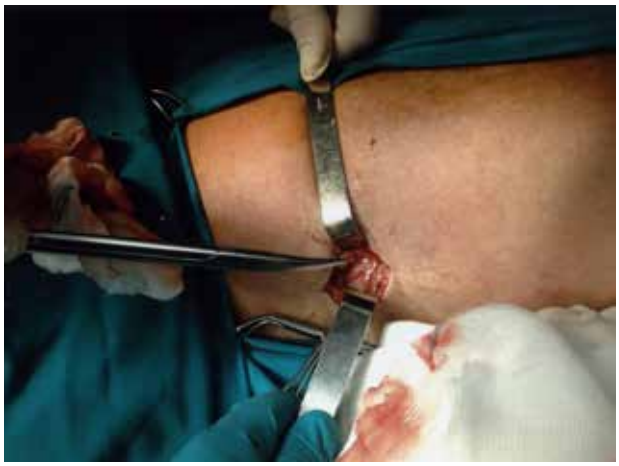

Fig.5. *Incision through skin and subcutaneous tissue down to fascia. There was immediate flow of pus. The "finger-test" was positive.*

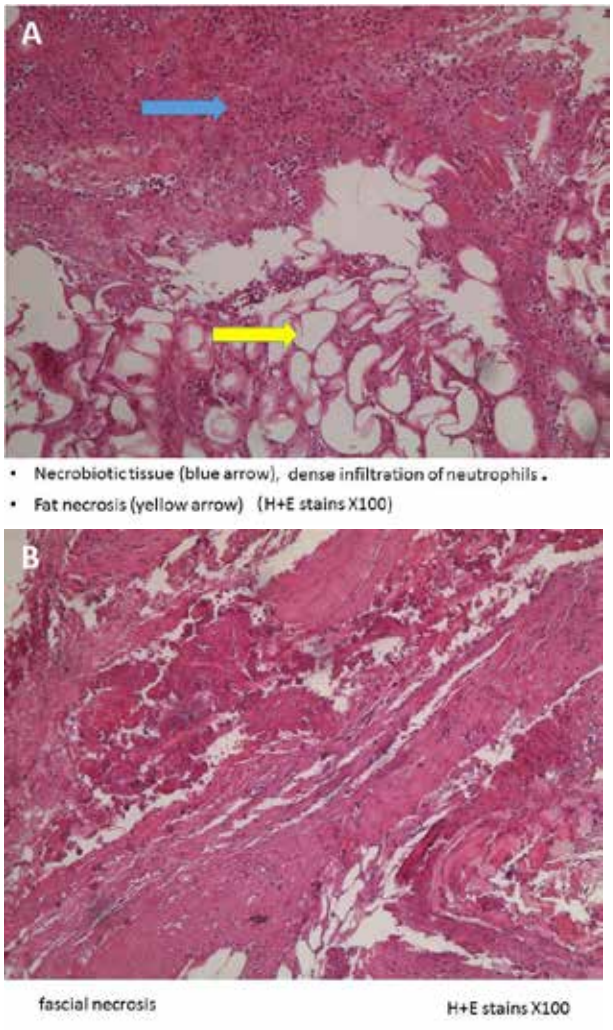

Fig.6. A. *Photomicrograph showing necrobiotic tissue (blue arrow), dense infiltration of neutrophils and fat necrosis (yellow arrow) (H&E stains x 100).* ***B.*** *Photomicrograph showing extensive fascial necrosis (H&E stains x 100).*

the enterobacteriaccae. Type II NF is a monobacterial infection caused by group A hemolytic streptococcus. Type III NF is caused by the marine Vibrio species. Type IV NF is caused by fungal cases of Candida and it is very rare (14).

The incidence of NF is low, 0.4 cases per 100,000 people (14). In the US, the annual age adjusted incidence was 4.3 invasive infections per 100,000 of the population (6). An increase, however, has been observed in Europe (UK), as well as in New Zealand. Brown et al (15) reported that the Health Protection Agency identified 1012 cases of invasive group A streptococcal infection (iGAS) between week 37, 2008 and week 20, 2009, compared to between 712 and 887 cases for the same period in the previous four years. Bodansky et al (16), in a more recent study reported that age-standardized incidence for NF patients requiring surgery increased from 4 to 20 per million across the study period (2002-2017). Das et al (17) observed a highly significant rise in annual incidence rates of NF in New Zealand from 0.18 to 1.69 per 100,000 person-years (1990-2006). Males seem to be more frequently affected than females (52.7% vs 47.3% - 11,042 patients) (16). The median age of patients is ca 60 years (range 44-60y) (16, 18).

In many cases of NF, an identifiable antecedent penetrating trauma or surgical procedure is evident. Surprisingly, the initial lesion can be often trivial, such as an insect bite, minor abrasion, boil, postoperative infection or injection site (e.g., subcutaneous insulin, illicit drugs) (19). Cheung et al (6) reported that sites of prior trauma and skin lesions were the two most common portals of entry (44.8% of patients). Furthermore, these infections can develop secondarily to minor blunt trauma, muscle strain or even spontaneously. Spontaneous occurrence is rare, with hematogenous or lymphatic spread responsible for the translocation of group A β hemolytic Streptococcus (GAS) (15). Although a minor muscle injury cannot be excluded in the

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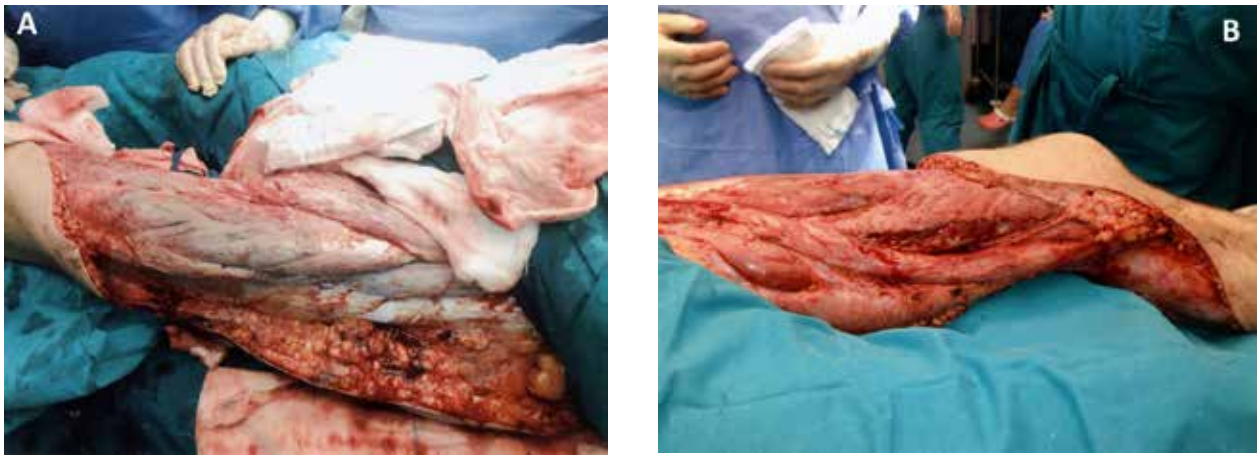

Fig.7 *Patient two after surgical debridement. A. Lateral aspect. B. Medial aspect.*

two patients presented here (gym, ski), no relevant symptoms were reported by either of them and no clinical signs indicative of a muscle injury could be identified. The most common presentation of GAS infection is with pharyngitis which accounts for up to 40% of cases seen by general practitioners in the United Kingdom (20). The majority of patients with NF, however, do not have preceding symptoms of pharyngitis or tonsillitis (21). The differences in severity of invasive streptococcal infections have been attributed to human leucocyte antigen class II allelic variation. This is due to their ability to regulate cytokine responses triggered by streptococcal super antigens (22). Both patients reported here had culture proven streptococcal pharyngitis which manifested a few days before onset of NF symptoms and signs. The latter were overlooked by general practitioners in both cases.

The clinical presentation of necrotising fasciitis entails progressive skin changes. Early on, only tenderness, erythema, warm skin and swelling are present, as was seen in both patients described here. Specific signs such as crepitus and blistering are rare. The average time of symptoms until hospital admission has been reported 4.1 days (8). In an American study on 198 patients, swelling was present in 75.0%, pain in 72.9%, and erythema in 66.3% (8). Foul discharge (46.8%), induration (45.3%), crepitus (36.5%), fever (31.6%), skin slough or necrosis (31.1%), blistering (23.7%), and skin discoloration (18.4%) occurred less frequently (8). In another study from India involving 75 patients, 91% presented with local tenderness, 99% with edema, 72% with erythema, 73% with ulceration and 72% with a purulent or serous discharge (23). Hypotension (systolic blood pressure < 90 mmHg) (see Case two) was reported in 11-33% (6, 8) and disorient-ation/mental obtundation in 17-24% (6, 8). At the initial stage, many patients are mistakenly diagnosed as having cellulitis due to overlapping diagnostic characteristics between cellulitis and NF. This results in delayed management. When critical skin ischemia occurs, blisters or bullae are formed. Blistering is due to ischemia-induced necrolysis as the invading organisms cause progressive thrombosis of vessels that penetrate the fascia to supply skin (24). As the disease progresses, skin lesions turn black and form a necrotic crust. The occurrence of tissue necrosis results in hypo- or anesthesia of the affected region due to nerve involvement (6). Tissue crepitation may be present due to gas production by aerobic and anaerobic bacteria. The skin eventually becomes hemorrhagic and gangrenous (6).

Diagnosis of NF, especially of the initial stage, is difficult due to its similar clinical presentation with other skin and soft tissue infections. Initial suspicion, however, is based on the clinical picture. The presence of severe pain, fever and thigh skin erythema without underlying hip pathology raised strong suspicion of a necrotising infection in our first patient, whereas the entire clinical picture of our second patient was indicative of necrotising fasciitis,

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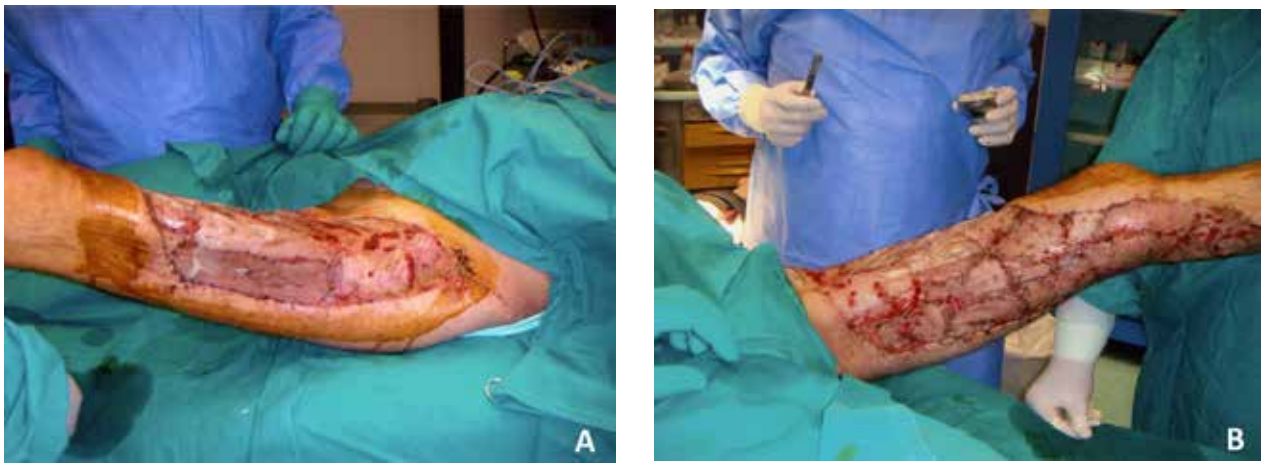

Fig.8. *Patient two after skin grafting of left thigh defect. Hypertrophic granulation tissue is seen at graft junctions. A. Lateral aspect. B. Medial aspect.*

despite the different opinion of the infections specialist. The Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC: C-reactive protein, white cell count, hemoglobin, sodium, creatinine, and glucose) has been proposed as a diagnostic tool for NF infection (24). Patients with a LRINEC score of > or = 6 should be carefully evaluated for the presence of NF; a score of > or = 8 is strongly predictive of this disease. The value of LRINEC has been validated by later studies even for patients with comorbid conditions (25, 26, 27). Su et al (25) reported that patients with a LRINEC score of > or = 6 have a higher rate of both amputation and mortality. Other authors observed that severe hypoalbuminemia, severe thrombocytopenia and increased banded forms of leucocytes are laboratory risk indicators of NF and predict a higher risk of death (28). Recently, serum procalcitonin has been suggested as a useful marker for differentiating NF from cellulitis. A cut-off value of 1.0 had a sensitivity of 88%, a specificity of 89%, a positive predictive value of 81%, and a negative predictive value of 93% (29). The most useful diagnostic imaging modality in the diagnosis of NF is MRI. Signs that support a diagnosis of NF include extensive involvement of the deep intermuscular fasciae (high sensitivity, low specificity), thickening to more than 3 mm, and partial or complete absence on post-gadolinium images of signal enhancement of the thickened fasciae (fairly high sensitivity and specificity) (30). Ultrasonography is not recommended in adults, as the infiltration of the hypodermis blocks ultrasound transmission (30). Imaging may help to confirm deep tissue involvement and to evaluate lesion spread, however, it should never delay emergency surgical treatment in patients in whom NF is strongly suspected (30, 31).

The "finger-test" and rapid frozen section biopsy examination have proved very useful in aiding diagnosis of patients presenting with suspected necrotising fasciitis in the early and intermediate stages (32, 33, 34). The test is performed in the following manner: the area of suspected involvement is infiltrated with local anesthesia and a 2-cm incision is made in the skin down to the deep fascia. Lack of bleeding is an ominous sign of a necrotising process. On many occasions, a "murky, dishwater fluid" has been noted in the wound (clear pus in Case 2 of the present study). A gentle probing maneuver with the index finger is performed at the level of the deep fascia. If the tissues dissect with minimal resistance, the finger-test is positive. Tissue biopsies are sent for frozen section analysis. The characteristic histologic findings include obliterative vasculitis of the subcu-taneous vessels, acute inflammation, and subcutaneous tissue necrosis (33). If the finger-test or the rapid frozen section analysis is positive or if the patient has pro-gressive clinical findings consistent with NF, he/she should be resuscitated and taken emergently to the operating theatre for surgical debridement.

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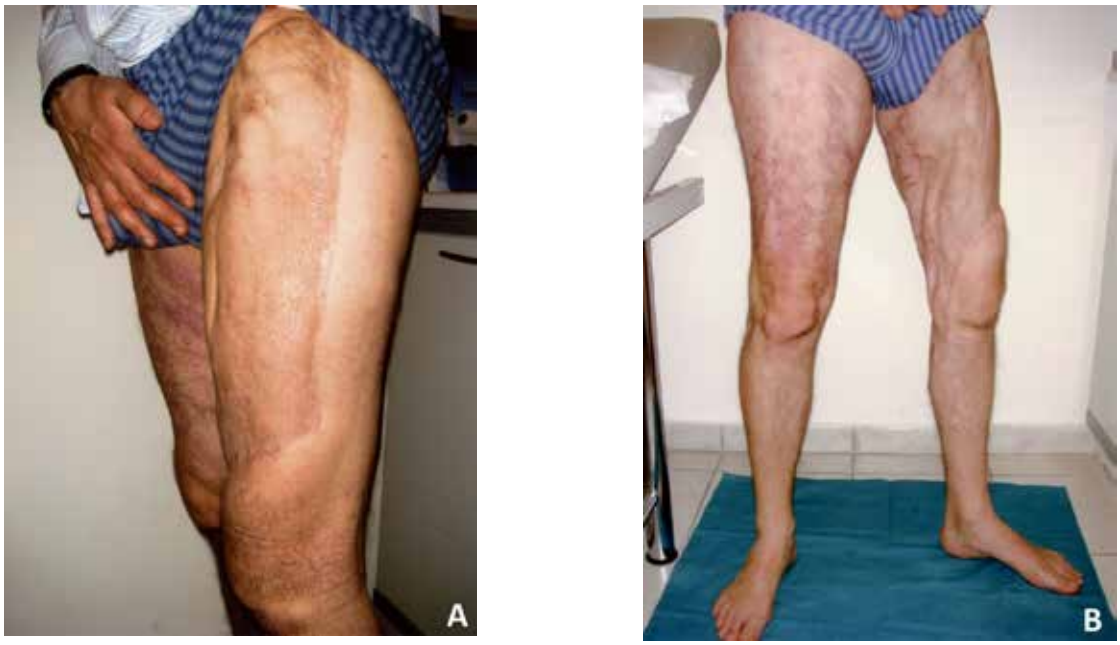

Fig.9. *Patient two one year postoperatively. A. Lateral aspect. B. Medial aspect.*

Necrotising fasciitis represents a surgical emergency. The large amount of necrotic tissue fuels a persistent septic state and recalcitrant hemodynamic instability. Whenever possible, aggressive resuscitation must be initiated immediately to maintain hemodynamic stability (19). However, one may not be able to completely stabilize the patient before surgery, in which case the anesthetist continues the resuscitative efforts intraoperatively (33). Surgical debridement of all obviously necrotic and poorly perfused tissues leads to more rapid overall clinical improvement. It is therefore essential that surgeons be consulted early in the care of these challenging patients. Early surgical debridement is a life-saving treatment (34, 35, 36). Furthermore, it may minimize tissue loss, eliminating the need for amputation of the extremity, which has been reported to be necessary in ca 22% of patients (6, 35, 36). There has been controversy regarding how much tissue should be initially excised because the skin may often appear normal. Andreasen et al (33) examined the normal-appearing tissues microscopically and found that they had extensive early vascular thrombosis and vasculitis, suggesting a high potential for full thickness loss. Therefore, these authors recommended wide, extensive debridement of all tissues that can be easily elevated off the deep fascia with gentle finger dissection. The wound must be inspected closely (usually daily), as hemodynamic instability usually persists postoperatively, and progressive skin necrosis may occur from infectious spread or hypoperfusion, as was observed in Case one of this study. Further debridement as often as necessary should be performed until the patient is fully stabilized and all necrotic tissue is removed. Once all of the affected tissues have been debrided, on an average between one and four debridements are necessary (19), the patient is asymptomatic and two consecutive tissue cultures are negative, reconstruction of the defect should be considered. Skin autografts are the best option for larger defects, whereas small defects (< 200cm²) in difficult sites (e.g. articular surfaces) can be covered with free tissue transfer (37).

When there is limited donor-site availability, alternatives to standard skin graft reconstruction include collagen-chondroitin scaffold (Integra artificial skin – Integra Life Sciences, Plainsboro, NJ, USA) or decellularized human dermis (Alloderm – Lifecell Corporation, Blanchburg, NJ, USA) (33, 38) or any other of the currently available skin replacement technologies (39). Median time to grafting

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has been reported 12 days (IQR 5 – 22) (40), which coincide with the time both our patients underwent the reconstructive procedure. One hundred percent graft take was observed in both patients and no further reconstructive procedures were necessary. Intense postoperative physical/kinesiotherapy enabled both patients to return to normal physical activities (walking, etc.-three months) and sports (six to eight months) after hospital discharge.

Irreversible necrotic changes following sepsis and failed multiple debridements necessitate limb amputation (6). In a recent Danish nationwide register – based cohort study, amputation occurred in 7% of the individuals (41). Khamnuan et al (42) reported a similar amputation rate (8.4% - 127/1,507 patients) in a study from Thailand. Predictive factors for amputation included gangrene (risk ratio RR 4.77), diabetes mellitus (RR 3.08), skin necrosis (RR 2.83), soft tissue swelling (RR 1.76), and serum creatinine values > 1.6 mg/dL on admission (RR 1.71). Another recent cohort multicenter prospective study from Scandinavia reported that amputation occurred in 22% of patients with NF of an extremity and was associated with higher lactate level (43). Horn et al (36) analyzed prospectively 446 patients with surgically confirmed NF. Twenty one percent of extremity NF patients required amputation. Age greater than 60 years, male sex, nonwhite race, diabetes, chronic wound as etiology, leg involvement, transfer status, and sodium < 130 mEq/L were independently associated with amputation. Patients with any of the above predictors should be monitored for progression and receive early aggressive treatment to avoid limb loss (36).

Immediate postoperative care is provided in the critical care setting. Fluid resuscitation, antibiotic therapy and nutritional support form an essential part of the postsurgical patient care. After the bacteria have been identified, therapy can usually be tailored further. Antibiotic therapy for necrotising infections in particular has not been studied in randomized controlled trials (44). The Surgical Infection Society and Infectious Disease Society of America guidelines both strongly recommend combination therapy with penicillin and clindamycin in necrotising soft tissue infections due to GAS (45, 46). No clinical trials have evaluated duration of therapy in NF (47). Guidelines suggest continuation of appropriate antibiotics for a minimum of 48 – 72 h after resolution of fever and other systemic signs of infection as well as hemodynamic stabilization (47).

Adjunctive medical treatments for NF have been utilized, the most common of which include intravenous immune globulin (IVIG) and hyperbaric oxygen. The proposed mechanism of action of IVIG relates to binding and inactivating circulating superantigens, thereby blunting the superantigen- mediated cytokine cascade. A propensity- matched analysis of administrative data from 130 US hospitals (48) and a RCT from Denmark (INSTINCT study) (49) found no benefit of IVIG on physical functioning or survival at 6 months. Hyperbaric oxygen is believed to potentially enhance oxygen delivery to hypoxic tissues surrounding areas of necrosis, directly killing anaerobic bacteria and improving leucocyte activity (50). Encouraging results were reported by Jallali et al (50), however, a more recent systematic literature review failed to locate relevant clinical evidence to support or refute the effectiveness of hyperbaric oxygen therapy in the management of necrotising fasciitis (51). Furthermore, the greatest barrier to practical use of hyperbaric oxygen in NF is the limited number of centers with hyperbaric chambers where critically ill patients can be adequately monitored (47).

Despite efforts to treat the rapid infective process, many patients still die through complications of sepsis (pneumonia, heart failure, metabolic disturbance) and finally multiorgan failure (6). It should be noted, however, that mortality rates, reported as high as 75% two decades ago (6), have been mitigated and currently range between 15 and 20% (18, 36, 40, 41, 42, 43). In a study of the US Multiple Cause of Death files (2003 – 2013), 9,781 NF – related deaths were identified corresponding to a crude mortality rate of 4.8 deaths/1,000,000 person – years. Diabetes mellitus, obesity and renal failure were significantly associated with NF-related death (52). Fatal cases of NF were more common among older individuals, and the greatest number of cases was observed among individuals aged 55 to 64 years (52). In another study, Ahn et al (53)

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reviewed retrospectively the American College of Surgeons – National Surgical Quality Improvement Program and found 674 patients with lower extremity NF. Although diabetes mellitus (DM) was associated with more amputations for lower extremity NF, patients with DM had lower mortality than non – DM patients in the bivariate analysis (53). Increased mortality has been associated with age > 60 years by most authors (34, 36, 41, 42, 43, 53). Other factors which have been associated with a higher mortality rate include higher lactate level (43), white blood cell count > $30x10^2$/ml and platelets < $150x10^3$/ml (36), systolic blood pressure < 90 mmHg and serum creatinine > 1.6 mg/dL (42), partial thromboplastin time > 38 seconds, and albumin > 2.0 mg/dL (53). Comorbid conditions (congestive heart failure, peripheral vascular disease, chronic kidney disease and cancer) were associated with higher in–hospital mortality (34, 40). Mortality rate has been shown to increase when patients are transferred from outside facilities (18), whereas admission to high-volume hospitals seem to be associated with improved survival (41).

The severity of NF and the aggressive treatment requirements put survivors at risk for significant long-term sequelae related to the trauma of both disease and treatment. While mortality rates have improved, long-term outcomes in survivors are poorly understood (54). Patients who have survived often suffer from functional impairment and altered body appearance. Pain medication and/or supportive devices are frequently required and the patients present with significant physical, psychological and relational sequelae at midterm follow-up (55). Hakkarainen et al (56) interviewed 18 NF survivors with a median follow-up of 4.2 years (range 3-6y) and identified increased value placed on life, some level of depression (related to external disfigurement), posttraumatic stress, pain, sexual difficulties, physical function (loss of mobility), behavioral changes, fear of infection, change in dress, and change in social activities (e.g., dance due to physical impairment). Both our patients initially reported fear of infection, temporary relational difficulties, and influenced societal factors, all of which were normalized at long term follow- up. Special attention which had been given to the reconstructive part of their treatment, and intensive active and passive physical therapy resulted in an acceptable appearance of the limb and near normal functionality (no oedema, ROM, muscular strength etc.) one year after hospital discharge.

The presentation of two cases of streptococcal pharyngitis and ensuing NF of the lower limb, no matter how rare, aims to alert clinicians to a high index of suspicion for necrotising fasciitis, which has an aggressive clinical course and can progress rapidly (within hours). Clinicians should have a high index of suspicion and a low threshold for surgical referral (11). Complaints of pain out of proportion to the visible findings or excruciating tenderness are clinical aids to early diagnosis. Upon admission, the general approach is to start empirical antibiotics, as most conditions will respond. Repeated physical examinations should be performed whilst maintaining a low threshold for a "finger test", tissue biopsy and surgery. It is safer to treat the ambiguous cases as necrotising fasciitis and manage them aggressively, as delay in treatment can be life threatening.

Conclusions

Streptococcal pharyngitis can, very seldom, lead to necrotizing fasciitis/myositis of the lower limb. Because of the potentially fatal course of NF, early diagnosis is the key to a favorable outcome. Laboratory findings (LRINEC score) and imaging may be useful, however, the diagnosis is a clinical one, and suspicion alone warrants early surgical consultation. The mainstay of treatment is immediate resuscitation of the patient, followed by aggressive surgical debridement and intravenous antibiotic therapy. Once the patient's condition has been stabilized, meticulous reconstruction of the defect followed by intensive physiotherapy is mandatory in order to ensure a better postoperative quality of life.

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Conflict of interest

No conflict of interest to declare.

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ACTA

YOUNG SCIENTISTS' PAGES

Adult Scoliosis: Therapeutic Approach and Spinal Pain Management

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ABSTRACT

Advancing adult scoliosis may lead in deterioration of patients' overall health and progressive disability. It can be a quite complex disorder to manage; however, nowadays there are several conservative and surgical therapeutic approaches. The aim of this study was to review the current literature concerning the therapeutic management of patients with adult scoliosis and the management of spinal pain that the majority of these patients experience. The review of the current literature was carried out by using the online PubMed database and the following keywords: ("adult" [MeSH Terms] AND ("scoliosis" [MeSH Terms] AND ("pain" [MeSH Terms] AND ("conservative treatment" [MeSH Terms] AND ("spinal fusion" [MeSH Terms]. The primary search recovered 3.941 publications. In the initial screening of abstracts and titles, 3,902 articles were excluded because of either irrelevant titles or not matching content. From the remaining 39 studies, in which the full text was assessed, 12 were rejected due to particular reasons. Finally, 27 studies were included in this review. In conclusion, a variety of therapeutic approaches for adult scoliosis exist. The type of treatment depends on various factors and has to be personalized. The prevailing aspect is that patients with moderate scoliosis should seek conservative treatment first, as long as there isn't any serious deterioration in their symptoms and quality of life. Conservative management should be exhausted before any decision for surgery is taken.

Key Words: adult, scoliosis, pain, conservative treatment, spinal fusion

Introduction

Scoliosis is described as a three-dimensional malformation of the spine. The typical method to measure the deformation of the spinal curvatures is the Cobb technique. A Cobb angle of ≥10 degrees clearly marks the presence of scoliosis [1, 2, 3]. Scoliosis can be classified into structural and non-structural or functional. Structural scoliosis is by far the most common type of scoliosis and it is characterized by a stiff lateral curvature of the spine that includes a component of rotation as well. The spinal deformation is permanent unless treated. The most common types of structural scoliosis are neuromuscular, congenital, adolescent idiopathic and degenerative or "de novo". Non-structural is the type of scoliosis that involves a non-permanent lateral curvature of the spine without spinal rotation. Non-structural or functional scoliosis is caused mainly in response to an underlying painful condition as muscle spasms, osteoid osteoma of the spine or appendicitis in order for the patient to maintain an antalgic position. Another common cause of functional scoliosis is leg length discrepancy. If the patient bends forward or

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is lying down the curve is most likely to disappear. In addition, during a radiographic assessment the curve can be corrected with lateral bending to the opposite side. Treating the underlying cause corrects this type of scoliosis [4].

Adult scoliosis can stem from different causes and has two basic types: adolescent idiopathic scoliosis that keeps evolving during adulthood and degenerative or "de novo" scoliosis that affects adults without scoliosis history and often manifests after the fourth decade of life. The yearly increase of the scoliotic curve is 1.6 degrees for degenerative and 0.24 degrees for idiopathic scoliosis [11]. Degenerative scoliosis is a result of the degeneration of spinal components such as facet joints and discs that occurs with aging and usually affects the lumbar and thoracolumbar spine [4-7]. A sufficient number of studies mention the high incidence of scoliosis in the adult population. Indeed, in the elderly population from the age of 60 years and over the incidence may be as high as 68% [5, 7-13]. Neuromuscular scoliosis can be due to central or peripheral neurologic conditions that have an effect on the developing spinal column. It can also develop from conditions that affect muscle tissue like arthrogryposis, muscular dystrophy and Duchenne myopathy. All these conditions can lead to muscular imbalance and atrophy of the spinal muscles. Aging is a major cause of deterioration of this condition [14, 15].

There are several similar symptoms between the different types of adult scoliosis. The leading symptom is back pain that mainly derives from insufficiency and contractions of the spinal and postural muscles. In addition, back pain can derive from the lack of equilibrium in the frontal or sagittal plane and the subsequent degeneration of spinal components such as the articular facets and the intervertebral discs [1]. Another cause of back pain could be the lack of lumbar lordosis [3, 11]. Although it has been shown that pain is not directly related with the scoliotic curve's magnitude and location, lumbar and thoracolumbar curves have increased risk to cause pain [3]. Patients with degenerative scoliosis experience back pain in a percentage of 40-90% [11]. Often, the pain can be detected along the side of the convexity [16]. Back pain is associated with lumbar radiculopathy in 47-78% of cases [1, 7, 16]. In addition, patients with adult scoliosis after the 6th decade of their life may also develop symptoms of spinal stenosis and myelopathy [4].

Treatment of adult scoliosis includes conservative and surgical methods of management. Pain management and improvement of physical ability and quality of life is always an important goal for any type of treatment. However, surgical treatment has different indications from conservative treatment. Stopping further development of the spinal deformity and restoring or avoiding feature neurologic defects are the main indications for surgical treatment [1]. Traditionally, patients with curves ≥45-50^{o} are in need of surgery, usually spinal fusion [2]. However, when there are no disabling symptoms the first choice is usually conservative treatment [5]. Conservative treatment typically consists of oral medications (non-steroidal anti-inflammatory drugs, opiates, amitriptyline, gabapentin, pregabalin), epidural injections, nerve blocks, physiotherapy, specific scoliosis and stabilization exercises and soft or rigid bracing [5, 6, 9, 17, 18, 19, 20].

The aim of this study was to review the current literature concerning the therapeutic management of patients with adult scoliosis and the management of spinal pain that the majority of these patients experience.

Discussion

A review of the current literature was carried out by using the online PubMed database and the following keywords: ("adult" [MeSH Terms] AND ("scoliosis" [MeSH Terms] AND ("pain" [MeSH Terms] AND ("conservative treatment" [MeSH Terms] AND ("spinal fusion" [MeSH Terms]. Inclusion criteria to the review were: studies from 2010 and on, review articles, systematic reviews, randomized controlled trials, prospective and retroprospective studies, pilot and cohort studies related to the therapeutic approach of adult scoliosis and spinal pain management. Articles in other than English language were excluded. The primary search recovered 3,941 publications. In the initial screening of abstracts and titles, 3,902 articles were excluded because of irrelevant titles and not matching content. From the remaining 39 studies in which the full text was assessed, 12 were rejected due to particular reasons. Finally, 27 studies were included in this review (Table 1).

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Bracing

Bracing is a treatment modality that seems to be used more and more as it is a non-invasive and inexpensive method to treat scoliosis. However, this conservative option is more popular and preferred in adolescence and childhood. Even though, in a recent study, adult patients suffering from idiopathic or degenerative lumbar scoliosis that were prescribed a custom-molded lumbar sacral orthosis (LSO) which had to be worn for at least 6 hours daily, showed a crucial deceleration of angular value ($p<0.0001$) [6]. In another study, adults with scoliosis suffering from chronic non-specific low back pain related to loss or reduction of lumbar lordosis seemed to benefit from lumbar bracing [3]. Furthermore, according to a recent review study, soft or rigid spinal bracing (with wearing prescription varying from 2 to 23 hours per day) used as monotherapy or in conjunction with physical therapy, led to moderate or significant pain relief as well as function improvement in patients with adult scoliosis. However, observations concerning the Cobb angle were various; curve magnitude improved moderately or significantly or progressed slower or not at all. Despite that fact, there were also cases that bracing didn't seem to affect the curve's progression [7]. In another recent study, peak scoliosis brace was found to be beneficial in reducing pain in adults with idiopathic scoliosis. After a four-week period of using the brace for 2-4 hours per day, 75% of patients noted some improvement regarding worst pain and leg pain and 65% noted improvement in chronic low back pain; however, the results were not statistically significant [13].

Exercising

Adults suffering from scoliosis with no critically important neurological symptoms or perdition of quality of life could manage their condition to a great degree by following an appropriate exercising program. However, there are certain limitations because exercising is recommended mainly in patients with adult idiopathic scoliosis (ADIS). On that note, several protocols of exercising have been studied such as asymmetric spinal stabilization exercises (ASSE), scoliosis specific exercises, SEAS (scientific exercise approach to scoliosis), Pilates method, Schroth technique as well as a multidisciplinary program that except of the physical training includes a psychological therapy. In a recent study, patients who followed a personalized program that depended on the curve's type and aimed in strengthening the muscles on the concaved zone of the scoliotic curve showed a significant improvement in Cobb angle mainly in prone position [17]. In another study, ADIS patients were assessed after a mean of two years of performing SEAS. The results showed a progress of scoliosis in less than 68% of the patients. In addition, there was an improvement in angular value ($p<0.05$) unrelated to the curvature's magnitude and location and unrelated to the age, gender and duration of treatment [18]. Furthermore, Schroth technique seems quite helpful when the curve's angle is 10-30^{o} and the exercise protocol is performed for at least 6 months in a row [19]. Moreover, a rehabilitation program for ADIS patients consisting of specialized exercises and cognitive behavioral therapy (CBT) seemed to be superior from a general physiotherapy program [20]. In another recent study, ADIS patients that followed the same program for 20 weeks seemed to have a significant improvement in domains like pain, disability, kinesiophobia, catastrophizing and quality of life. However, regarding the clinical deformity, there was improvement but not clinically significant. The benefits of this approach were present for one year at the minimum [21]. Similar benefits have been reported in women with thoraco-lumbar scoliosis that followed a therapeutic intervention based on Pilates Method. In these women, scoliosis angular values decreased by 38%, stretchiness improved by 80% and pain was critically decreased by 60% [22].

Operative approach

Surgery is usually considered when all conservative measures have failed. When the patient is not satisfied with their current condition and their symptoms insist and cause deterioration of their quality of life, surgical options have to be discussed considering all the benefits, the disadvantages and the possible complications. The type of surgical technique used depends on patient's age and clinical condition and on surgeon's preference.

The main goals of surgical treatment are pain reduction and improvement of deformity principally on the sagittal plane. Spinal fusion, using pedicle screws

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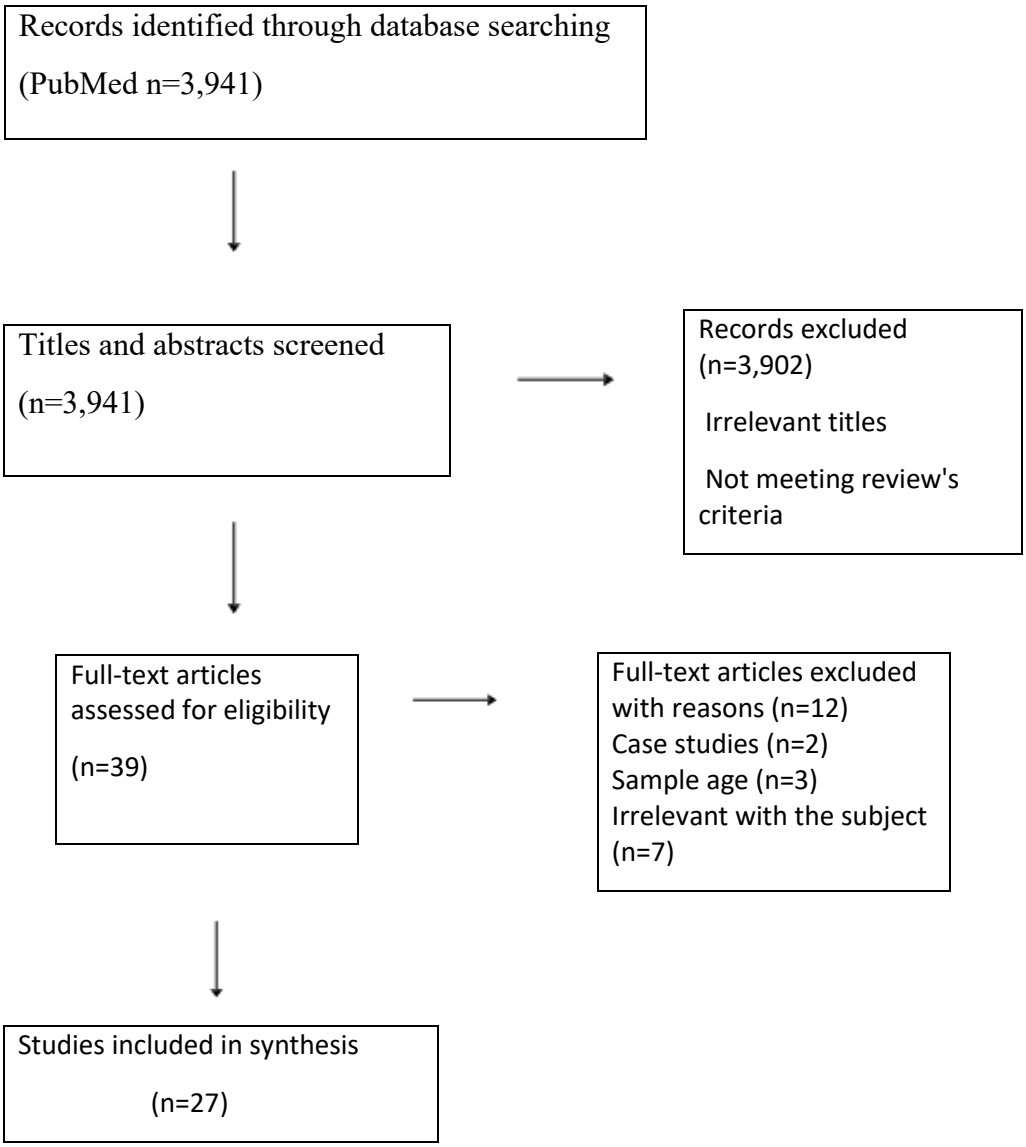
Figure 1. Flowchart



with or without the use of cages and grafts, through a posterior or/and an anterior approach is the most commonly used surgical technique. Surgical treatment appears to have better results than conservative treatment. According to a recent study including 49 patients operated for degenerative scoliosis, on the eight years follow up 23% of patients had excellent results, 29% had good, 34% had good enough and 14% had inadequate results. In addition, pain was improved in the visual analog scale (VAS) from 7 to 2 and Cobb angle was improved approximately by 12° [1]. Similar results have been reported in another study including patients over 75 years old who underwent spinal reconstructive surgery. On the two years follow up, all patients had a significant improvement in radiographic evaluation and in Health-related quality of life (HRQOL), as well as in pain and disability. In contrast, conservatively treated patients did not show any improvement ($p>0.05$) [12]. Moreover, in another recent study, patients with symptomatic lumbar scoliosis who underwent spinal fusion, had better results than patients who followed a conserv-

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ative protocol with physical therapy, facet injections, oral administration of different medications (non-steroidal anti-inflammatory drugs, opioids, gabapentin) and nerve root injections for back and leg pain management. At the two years follow up, Oswestry Disability Index (ODI) and Scoliosis Research Society-22 Score (SRS-22) were more improved ($p<0.001$) in the operative group [23]. Even though patients that chose to proceed with surgery were in worse clinical condition than those who preferred the conservative approach, at the two years follow up they showed a significant improvement in domains like pain, disability and quality of life [24, 25].

Pharmacological Approach

Adults with scoliosis often suffer from persistent back or leg pain that can lead to disability. Constant pain is usually managed with a combination of oral medications as non-steroidal anti- inflammatory drugs, antidepressants and opiates administered for only a short period of time [26]. Indeed, narcotic analgesics, muscle relaxants and tricyclic antidepressants can be useful in pain management, especially of night pain. Gabapentin seems to be beneficial in managing neurogenic pain and it seems to be well tolerated by elderly population [27]. However, all these drugs come along with side effects such as gastrointestinal dysfunction and acid-peptic disease and must be used with caution. Moreover, focused epidural, facet injections or nerve root blocks can be used both for diagnostic and pain-relieving reasons because they can help patients localize the source of their pain [5, 9].

In conclusion, a variety of therapeutic approaches for adult scoliosis exist. The type of treatment depends on various factors and has to be patient specific. The prevailing aspect is that patients with moderate scoliosis should seek conservative treatment first, as long as there isn't any serious deterioration in their symptoms or quality of life. Conservative management should be exhausted before any decision for surgery is taken. The surgeon has to assess the benefits and risks of such decision taking into consideration patient's best interests. A

Conflict of interest

The authors declare no conflict of interest.

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Pharmaceutical treatment of spinal cord injuries in the acute phase

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ABSTRACT

The initial treatment of spinal cord injuries during the acute phase is very important as it largely determines the prognosis of patients. The purpose of this study is to review the medical interventions in the acute phase after spinal cord injury. In the PUBMED database, a search was performed with the following keywords: ("methylprednisolone" OR "riluzole" OR "rho inhibitor" OR "cethrin" OR "G-CSF" OR "minocycline" OR "TRH" OR "GM-1") AND "spinal cord injury". Only prospective, randomized, placebo-controlled studies written in English were included in the study. Studies published in non-English language, incident reports, retrospective studies, observational studies, systematic reviews, experimental animal studies were excluded from the review. Finally, 17 studies were included in the present review, including the following drugs: methylprednisolone (8 studies), rizulole (1 study), G-CSF (1 study), rho inhibitors (2 studies), minocycline (1 study), TRH (1 study), ganglioside GM-1 (2 studies), combination of progesterone and vitamin D (1 study). There is currently no drug with a high level of evidence that can be administered against acute spinal cord injuries. There is not enough convincing evidence that high doses of methylprednisolone for acute spinal cord injury are beneficial, given the high rate of complications. The role of steroids in acute spinal cord injury remains unclear, and some studies have shown that the risks of steroids outweigh the benefits. With many promising therapeutic agents and strategies being studied in ongoing trials for spinal cord injury, there is great hope of finding an effective treatment that would make significant progress while also benefiting patients with other neurological conditions.

Key Words: Spinal Cord Injury, Drug Therapy, Acute Phase

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Introduction

Acute spinal cord injury (ASCI) is, to this day, known to be an incurable condition. ASCIs result in a high morbidity rate and can also present an increased risk of death. The initial treatment of spinal cord injuries during the acute phase is very important as it largely determines the prognosis of patients. While clinical management of patients with ASCI is likely to have made considerable progress with medical advancement, the development of neural regeneration therapy has yet to be effectively implemented. Clinical research on efficacy of pharmacological treatment for ASCI reveals minimal and controversial clinical evidence [1, 2]. The purpose of this study is to review the medical interventions in the acute phase after spinal cord injury.

Materials & Methods

Based on the literature, we focused on the following drugs: methylprednisolone, riluzole, granulocyte colony stimulating agent, rho inhibitors, TRH, ganglioside GM-1, minocycline and others. In the PUBMED database, a search was performed with the following keywords: ("methylprednisolone" OR "riluzole" OR "rho inhibitor" OR "cethrin" OR "G-CSF" OR "minocycline" OR "TRH" OR "GM-1") AND" spinal cord injury". Only prospective, randomized, placebo-controlled studies written in English were included in the study. Studies published in non-English language, case reports, retrospective studies, observational studies, systematic reviews and animal studies were excluded from the review.

Results

As shown in the flowchart below (Figure 1), search results included 988 papers. After checking titles and abstracts and applying a filter that included only prospective, randomized, double-blind studies, 932 articles were rejected. From the individual analysis of the studies references another 1 study emerged, while 40 studies were excluded for specific reasons. Finally, 17 studies were included in the present review, including the following drugs: methylprednisolone (8 studies), rizulole (1 study), G-CSF (1 study), rho inhibitors (2 studies), minocycline (1 study), TRH (1 study), ganglioside GM-1 (2 studies), combination of progesterone and vitamin D (1 study).

Discussion

Steroids

Methylprednisolone is the only medication recommended to improve patients' neurological outcomes with acute, nonpenetrating ASCI in randomized clinical trials. The objective evidence for the effectiveness of glucocorticoids in acute ASCI, however, is limited and, to many, unconvincing. In animal studies, glucocorticoids administration after spinal cord injury reduces edema, avoids intracellular potassium loss, and promotes neurological regeneration. Administration within the first eight hours after damage showed the best outcomes [3]. Some scholars suggest that the vital effect of methylprednisolone on the regeneration of the spinal cord was the suppression of lipid peroxidation and that late administration of steroids could have no impact on lipid peroxidation and could interfere with regenerative processes [4].

NASCIS [5] was a multi-center (included nine hospitals) double-blind, randomized trial that was conducted to examine the efficacy of a high dose of methylprednisolone (1000 mg bolus and daily after that for ten days—250 mg every 6 hours in 165 patients, a total of 11,000 mg) compared with the standard dose of methylprednisolone (100 mg bolus and daily after that for ten days —25 mg every 6 hours in 165 patients, a total of 1100 mg). A total of 330 patients with acute spinal column injury were evaluated and assessed after six weeks and six months of injury. Inclusion criteria were any loss of sensation or motor function below the lesion. Exclusion criteria were nerve root injury, equine cauda injury alone, admittance to the center >48 hours after injury, use of steroids before admission, severe comorbidity, other life-threatening conditions, patients younger than 13 years old, failure of consent, pregnancy, diabetes, severe vascular disease, gastrointestinal bleeding, or vascular disease. At six weeks, 47 patients were not evaluated:

- Twenty-six patients had died.
- Eighteen were unavailable for follow-up.
- Three patients had incomplete neurological examinations.

At six months, 179 patients were evaluated (91 high-dose and 88 low-dose). They reported no statistical difference in their neurological recovery of motor func-

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tion, pinprick, and light touch sensation between the two groups at six weeks or six months. The lack of a treatment effect was not correlated to the severity of the initial trauma or the time from injury to starting treatment. Although not statistically significant, early case fatality was more remarkable in the high-dose protocol, with a higher relative risk for wound infections.

The same lack of statistical significance between the two regimen groups was shown in the 1-year follow-up results that were published by the same authors [4]. Adjusting for potential confounding factors, there was no significant difference considering the neurological recovery of motor function, pinprick response, or touch sensation between the groups (the same findings of the first study). Case fatality rate was 10.7% and did not associate with steroid doses. None of the deaths could be linked to steroid treatment, according to the authors.

Bracken et al completed a second multi-center randomized, double-blind clinical trial in North America (NASCIS II) investigating the effectiveness and safety of methylprednisolone and naloxone in patients with acute spinal injury (95 percent were treated within 14 hours of injury). Methylprednisolone was administered to 162 patients in bolus (30 mg/kg followed by an infusion of 5.4 mg/kg/h for 23 h); naloxone was administered to 154 patients (5.4 mg/kg bolus followed by an infusion of 4 mg/kg/23 h), and 171 patients received placebo. Patients were assigned to groups within 12 hours of the diagnosis of SCI [6]. Neurological assessment was conducted at six weeks and six months after injury. Authors recorded that, at six months, patients treated with methylprednisolone had a substantial improvement in motor control relative to placebo within 8 hours of their injury, as well as an improvement in the perception of pinprick and touch. There was also some neurological recovery in the steroid cohort relative to naloxone or placebo. The naloxone or methylprednisolone cohort's findings after 8 hours of injury did not significantly differ in their neurological outcomes from those for placebo. This research introduced the first guideline regimen for the use of methylprednisolone.

The research group published data of one year of follow-up to the NASCIS II group [4]. The same improvement in recovery following administration of methylprednisolone was observed one year after the initial injury. Patients receiving methylprednisolone (P = 0.08) or naloxone (P = 0.1) after 8 hours of injury had less motor function than those receiving placebo. In all cohorts, adverse effects were similar. The authors suggested that methylprednisolone should be indicated for acute TSCI when started within 8 hours of injury.

The third NASCI-III trial [7] also recorded enhanced motor recovery in patients receiving methylprednisolone therapy within 3–8 h of ASCI and explicitly observed that this correlation was present at six weeks and six months (long-term follow-up) in patients receiving extended methylprednisone therapy (48 h) compared to those receiving a shorter treatment period (24h). Adverse effects were similar between the three groups, with some exceptions: severe sepsis reported in 2.6 percent of patients in the 48-hour MP treatment group compared to 0 percent in the 48-hour tirilazad group and0.6 percent in the 24-hour MP group (P = 0.07) and severe pneumonia reported in 5.8 percent in the 48-hour MP, 0.6 percent in the tirilazad group and 2 percent in the 48-hour MP group. Survival was similar in the three groups. They concluded that a substantial change in motor control was observed at six weeks and six months in the MP-receiving community for 48 hours compared to 24 hours when care began 3–8 hours after injury. In the first 3 hours of therapy, patients had precisely the same recovery pattern in the three groups. Although statistically meaningful, the differences in motor function were slight and usually limited to upper body function.

Bracken et al [8] announced the findings of a 1-year follow-up of a multi-center randomized, double-blind clinical trial in North America (NASCIS III). According to the authors, the results endorsed the 48-hour methylprednisolone regimen in patients treated between 3 and 8 hours after injury, but this could require caution due to a higher risk of pneumonia and respiratory complications. More deaths from pneumonia and respiratory distress syndromes were found in the 48-hour MP regimen and the tirilazad group.

A randomized controlled trial by Wang et al concluded that intermittent methylprednisolone infusion was effective in treating ASCIs, complicated by incomplete paraplegia, with a low incidence of adverse re-

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actions [9]. On the contrary, Pointillard et al found no clinical benefit of the use of methylprednisolone in acute management of SCI [10]. Elderly patients with cervical SCI may be more likely to have side effects after high-dose methylprednisolone and therefore deserve special care [11].

Riluzole

Riluzole is a benzothiazole that inhibits voltage-gated sodium channels and glutamate release and is currently the only licensed medication for treating amyotrophic lateral sclerosis. Riluzole works by blocking the sodium channels in neurons and may prevent increases in the intracellular concentration of sodium, finally leading theoretically to cellular death inhibition in ASCI. Grossman et al [12] conducted the first prospective, multi-center, phase I trial of riluzole safety and pharmacokinetics for ASCI. Riluzole was administered every 12 hours either orally or by nasogastric tube, within 12 hours after injury. The control group received the standard of care but no riluzole. Mean motor score for cervical injury patients treated with riluzole increased from admission to 90 days, compared to control patients, representing a statistically significant difference.

Rho-inhibitors

Following ASCI, Rho activation contributes to the collapse of axonal growth cones, axonal regeneration failure, and neuronal loss. Cethrin (VX-210) is a recombinant inhibitor of Rho that has been shown to promote axonal outgrowth on inhibitory substrates both *in vitro* and *in vivo*. Fehlings et al conducted a phase I/IIa clinical study to examine the safety and tolerability of Cethrin for acute SCI. No serious adverse events were noted in this study. The most considerable change in motor score was observed among cervical patients treated with Cethrin [13]. A subsequent, randomized, double-blind, placebo-controlled phase 2b/3 study [14] that evaluated the efficacy and safety of local delivery of Rho inhibitor VX-210 9 mg at the site of the injury during spinal decompression/stabilization surgery within 72 hours after injury in patients after acute traumatic cervical SCI, was ended prematurely after the preliminary results met the predefined futility stopping rule.

Granulocyte Colony-Stimulating Factor

Granulocyte Colony-Stimulating Factor (G-CSF) is a significant growth factor in the activation and division of granulocyte colonies in the bone marrow. Several clinical studies have been performed to examine the impact of G-CSF on acute SCI. Inada et al [15] performed a prospective, non-randomized, controlled, multi-center clinical trial to investigate the neuroprotective effects of G-CSF on acute SCI. Patients were split into two cohorts. G-CSF was intravenously initiated for five straight days within 48 hours of injury in the G-CSF group. Patients in the monitoring community were handled equally, except for G-CSF management. A substantial increase in the ASIA score was observed in the G-CSF group 1 week after administration relative to the control group. Some random changes in the motor score were also observed in the control group, but the G-CSF group's substantial improvement was retained until one year of follow-up.

Minocycline

Minocycline is a tetracycline antibiotic that has neuroprotective and anti-inflammatory effects. Casha et al [16] performed a single-center, placebo-controlled, double-blind clinical trial to determine the effectiveness and safety of intravenous minocycline within 12 hours of ASCI. Twenty-seven patients were assigned to received minocycline, and 25 received a placebo. Patients treated with minocycline demonstrated better motor recovery compared to control. Although no distinction in recovery was noted with thoracic SCI, statistical significance was recognized in the subpopulation with cervical injury. The study revealed a tendency to improve motor scores in incomplete cervical SCI in the absence of any significant adverse effects.

TRH

Thyrotropin-releasing hormone (TRH) is a hormone produced by the hypothalamus that stimulates the release of thyroid stimulating hormone (TSH) and prolactin from the pituitary gland. TRH has been used as an anti-aging agent in experimental animals and has a wide range of actions suggesting that TRH plays a fundamental role in regulating metabolic and hormonal functions [17]. In a randomized-controlled trial, in 20 ASCI patients, TRH treatment was associated with sig-

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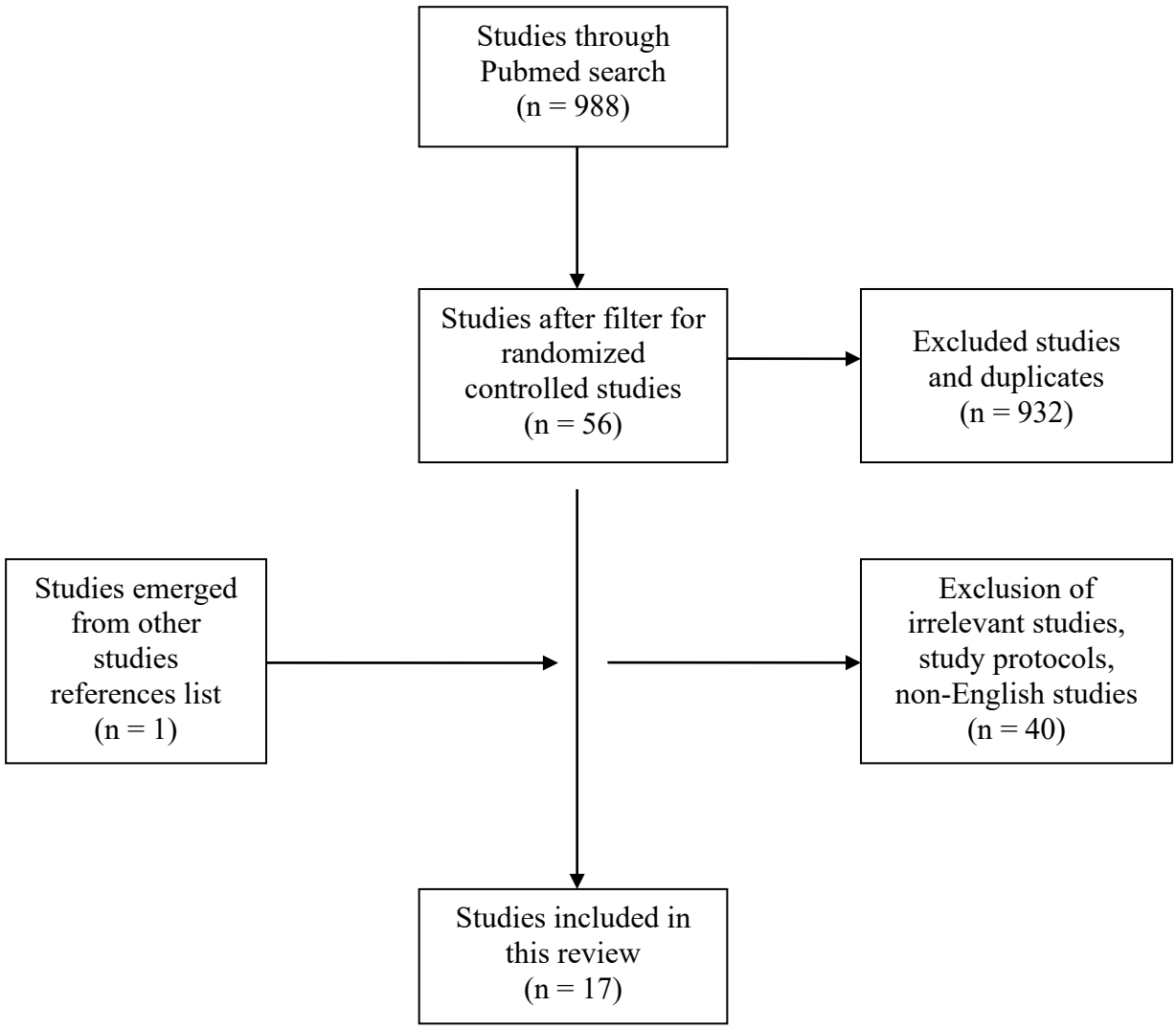
Figure 1. Flowchart



nificantly higher motor and sensory scores compared with placebo treatment [18].

Ganglioside GM-1

GM-1 ganglioside is a glycosphingolipid found in neuronal membranes that binds to secondary proteins that regulate signaling pathways involved in differentiation, regeneration, neuronal apoptosis, and neuroplasticity. A prospective, randomized, double-blind study of GM-1 ganglioside by Geisler et al in 37 patients with SCI showed significant improvement in mobility. Improvement mainly in lower limb function was observed only 48 hours after treatment [19]. These findings led to a large phase III trial in more than 750 patients at 28 institutions published by Geisler et al in 2001. However, the results of this study failed to achieve their ambitious primary outcome. The study showed that patients had improvements in the recovery of bowel and bladder function. Patients in both groups achieved significant improvement in functional independence.

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A major study error was the delay in GM-1 treatment, as most patients received methylprednisolone for the first time as part of their clinical treatment [20].

Progesterone and vitamin D

Aminmansour et al published a prospective, randomized clinical trial involving 64 adult patients with ASCI admitted to hospital within 8 hours of injury. All patients received methylprednisolone upon administration according to the protocol (30 mg / kg as bolus dose and 15 mg / kg every 3 hours to 24 hours). Patients were randomized to receive an intramuscular injection of 0.5 mg / kg progesterone twice daily and 5 μg / kg orally of vitamin D3 twice daily for up to 5 days (n = 32) or placebo (n = 32). Patients who received progesterone and vitamin D had significantly higher motor scores and sensory function after 6 months of treatment. Those treated within 4 hours of injury had significantly improved mobility and sensory function 6 months after treatment in the progesterone and vitamin D groups. The researchers concluded that administration of progesterone and vitamin D in the acute phase of traumatic spinal cord injury was associated with better functional recovery and outcome [21].

Conclusions

There is currently no drug with a high level of evidence that can be administered against acute spinal cord injuries. There is not enough convincing evidence that high doses of methylprednisolone for acute spinal cord injury are beneficial, given the high rate of complications. The role of steroids in acute spinal cord injury remains unclear, and some studies have shown that the risks of steroids outweigh the benefits. With many promising therapeutic agents and strategies being studied in ongoing trials for spinal cord injury, there is great hope of finding an effective treatment that would make significant progress while also benefiting patients with other neurological conditions.

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Injuries of the cervicothoracic junction with neurological signs: choice of spinal fusion and association with neurological and functional rehabilitation

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ABSTRACT

Injuries of the cervicothoracic junction (CTJ) are demanding with high rate of neurological complications. Due to its unique and diverse anatomical characteristics, the approach of CTJ for stabilization is challenging. The purpose of this study is to review the neurological and functional outcome of the spinal fusion in CTJ injuries with neurological signs. This is a simple literature review using the Pubmed internet database. Papers were searched with the use of the following keywords: ("cervicothoracic" OR "C7-T1") AND ("injury" OR "fracture" OR "dislocation" OR "spondylolisthesis") AND ("fusion" OR "fixation" OR "instrumentation"). The search retrieved a total of 199 papers (see flowchart). After screening of titles and abstracts, 158 articles were rejected. Of the 41 publications evaluated, 25 were rejected, leaving 16 studies for the present review. There were 3 prospective studies, 4 retrospective studies and 9 case reports. The evolution of surgical techniques and hardware has facilitated the approach and the instrumentation of the CTJ, allowing for low profile, rigid fixation. Complications of operations around the CTJ are frequent and the associated morbidity is significant. Appropriate training along with meticulous preoperative planning, surgical technique and postoperative care are essential for the prevention of these complications. However, optimal surgical procedure has not yet been clarified. More high-quality studies are needed to fully elucidate the best fusion method and approach in order to maximize the benefit for the treatment of these patients.

Key Words: Cervicothoracic junction spinal injury, Spinal fusion

Introduction

The cervicothoracic junction (CTJ) includes the C7 vertebra, the T1 vertebra, the C7 – T1 intervertebral disc and the adjacent ligaments. Representing the connection between the fairly mobile and lordotic cervical spine and the fairly rigid and kyphotic thoracic spine, it possesses unique biomechanical properties [1]. The thoracic spine has limited mobility because of the rib cage, exerting significant stress on the CTJ in the static and dynamic states. CTJ is vulnerable to instability be-

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cause of traumatic disruptions to associated structures causing significant and devastating spinal cord injury (SCI).

CTJ injuries represent 2% - 9% of all cervical spinal injuries. Their diagnosis, based on plain x-rays, is difficult, as the region is often obstructed by the shoulders [2-3]. So, in case a CTJ injury is suspected, a CT or MRI of the cervical spine should always be performed. CTJ injuries usually include fractures or dislocations; most commonly ligamentous injuries, burst fractures, and facet fractures [4]. Neurologic symptoms due to CTJ injuries are common, probably due to the small canal size of the CTJ, and vascular insufficiency [5].

Established management of CTJ injuries usually involves initial closed reduction, followed by fusion with instrumentation. Spinal fusion is usually performed within the first 3 days of injury [6]. Due to its unique and diverse anatomical characteristics, the approach of CTJ for stabilization is challenging. Anterior access is difficult, because of the deep location of the C7 and T1 vertebral body and the presence of multiple vital organs and blood vessels. The choice of anterior versus posterior stabilization depends on the surgeon's choice as well as on the pathologic findings of fractures [7]. The gold standard approach for fixation of CTJ injuries is through a posterior approach and this may be combined with anterior fixation [5]. Although some studies have shown that posterior-only fixation may be sufficient to stabilize CTJ injuries that include the anterior column, such as burst fractures, cadaveric studies have shown that in a 3-column injury, posterior fixation is not sufficient to restore the innate spinal stiffness [8]. Other biomechanincal studies have observed that a 3-column CTJ injury may be fixed by posterior-only instrumentation, with the addition of 2 cross-links [9]. So, the optimal way of spinal fusion for CTJ injuries is a matter of debate.

The purpose of this study is to review the neurological and functional outcome of the spinal fusion in CTJ injuries with neurological signs.

Material and method

This is a simple literature review using the Pubmed internet database. Papers were searched with the use of the following keywords: ("cervicothoracic" OR "C7-T1") AND ("injury" OR "fracture" OR "dislocation" OR "spondylolisthesis") AND ("fusion" OR "fixation" OR "instrumentation")

Results

The search retrieved a total of 199 papers (see figure 1). After screening of titles and abstracts, 158 articles were rejected. Of the 41 publications evaluated, 25 were rejected, leaving 16 studies for the present review. There were 3 prospective studies, 4 retrospective studies and 9 case reports.

No matter what surgical fusion technique is chosen, the primary aims are similar: stable internal fixation, placement of appropriate bone grafts, restoration of acceptable anatomic position, and decompression of neural structures. As a result of CTJ anatomical issues, initial attempts of CTJ fusion was based on spinous process wiring and lamina hooks rather than pedicle screws [10-11]. However, failure of fusion was frequent, as wiring did not provide the same stability as a rod or plate system. Moreover, both the spinous processes and the laminae are often removed during spinal surgery. A lamina hook may intrude into the spinal canal, in patients with spinal stenosis [10]. Screw-rod systems have provided strong fixation to the CTJ in biomechanical studies [8, 12-13]. Modern rod-screw systems are flexible enough and may achieve immediate rigid internal fixation with high rates of fusion. Rod-wire systems remain a simple, low-cost, and low-profile way of achieving CTJ fixation. [6].

Cadaveric studies have shown that C7 pedicle screw fixation is superior compared with lateral mass fixation at C7 in all biomechanical tests, providing high stiffness for stabilizing the CTJ [12]. The risks of medial or inferior C7 pedicle violation and associated neurologic injury must be balanced with the risk of injury or construct failure secondary to poor fixation in the C7 lateral mass [14]. The use of pedicle screws and lateral mass fixation at the CTJ is safe with a reported incidence of breaching of the pedicle to be estimated at 3% - 9%, while reported incidence of radiculopathy is 1% - 2% [15-16]. As a result, the possibility of a stiff and stable fusion of the CTJ region is increased. The concept of anterior instrumentation and fusion is performed less frequently at the CTJ region. Both cadaveric and clinical studies suggest that the results of such techniques are inferior to techniques that use posterior

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only or anteriorposterior fixation [17-18].

Prospective studies

The outcomes of plate screw fixation of the CTJ have been documented in separate studies. A prospective study by Anderson *et al* reported the efficacy of posterior spinal fusion with AO reconstruction plates and autogenous bone graft. Among the studied patients, two suffered from C7-T1 injury and associated tetraplegia and were treated with a C5-T1 or C5-T2 fusion. After a 17.8 months follow-up, one of the two patients showed significant neurological improvement [19].

A more recent prospective multicenter study by Ramieri et al, included 21 patients with CTJ injury. There were 8 ASIA A, 2 ASIA B, 6 ASIA C and 5 ASIA D patients. Using the combination of cervical lateral mass screws, thoracic pedicle screws and hooks, 16 patients were managed with posterior fixation and fusion, 3 patients underwent posterior fixation and fusion along with anterior body replacement and 2 patients received anterior body replacement alone. Eight patients experienced neurological improvement, 12 patients remained with the same neurological deficit and one polytrauma patient died because of severe brain injuries. Authors concluded that there is no type of instrumentation more effective than other [20].

When patients with ankylosing spondylitis, sustain a CTJ fracture, they are at a high risk of developing complications. A prospective cohort study by Robinson et al included 41 patients with CTJ fractures related to ankylosing spondylitis. All patients were treated with posterior fusion and instrumentation and were followed up for 2 years. Mean survival was 52 months, affected by patient age, sex, smoking, and SCI. Complication included postoperative infections (n = 5), respiratory tract infections (n = 3) and cerebrovascular fluid leakage (n = 1) [21].

Retrospective studies

Another retrospective study by Chapman *et al* reported 14 patients with traumatic instability of C7-T4 region and associated SCIs, which were treated with posterior AO reconstruction plate and screw fixation and fusion between the lower cervical and upper thoracic spine involving two to three levels for a burst fracture but more in case of ligamentous injuries. Preoperatively, 7 patients had a complete and 7 patients had an incomplete SCI. All patients achieved a solid arthrodesis based on flexion-extension radiographs. All cases of incomplete tetraplegia improved at least one Frankel grade, while 2 patients with complete tetraplegia experienced neurological improvement. There were no neurovascular, pulmonary or hardware complications [22].

A retrospective study by An et al included 15 patients with traumatic CTJ injuries (10 C7 fractures, 4 C7-T1 dislocations, 1 T1 fracture). Among them, there were 10 complete SCIs, 4 incomplete SCIs, while one patient had a root deficit. Ten patients underwent posterior fusion, while 5 patients underwent combined fusion and corpectomy, with anterior approach. Reported results were excellent in 1 patient, good in 10 patients, fair in patients and poor in 1 patient. Patients with complete tetraplegia had no appreciable improvement in neurological function. Half of the patients with incomplete lesions improved. The authors observed the occurrence of complications, including C6–C7 subluxation after C7–T2 fusion, pseudomeningocele, vocal cord paralysis, dysphagia, and Horner's syndrome. Other complications included wound infections, urinary and respiratory tract infections and deep vein thrombosis [1].

Another retrospective study by Sapkas et al included 6 patients with C7-T1 fracture / dislocation. Two patients had incomplete SCI, one patient had a complete SCI, whereas 3 patients had root deficits. All patients underwent laminectomy and posterior fusion with various implants such as plates, clamps and wires. The reported postoperative results were excellent (n = 2), good (n = 2) and fair (n = 2). After 22 months follow-up, patients with incomplete SCI significantly improved their neurologic function by at least one or two Frankel grades. All patients with root deficits improved, and at nearly 6 months post-operatively they were restored completely. There was no improvement in neurologic function in the patient with complete SCI [5].

In 2006, Lenoir et al published a retrospective study including 30 patients (22 male – 8 female) who underwent surgical treatment for unstable fracture at the CTJ. Lesion level was C7 (n = 18), T1 (n = 5), T2 (n = 2) and T3 (n = 5). Upon initial clinical evaluation, patients were classified as Frankel A (n = 16), Frankel B (n = 6),

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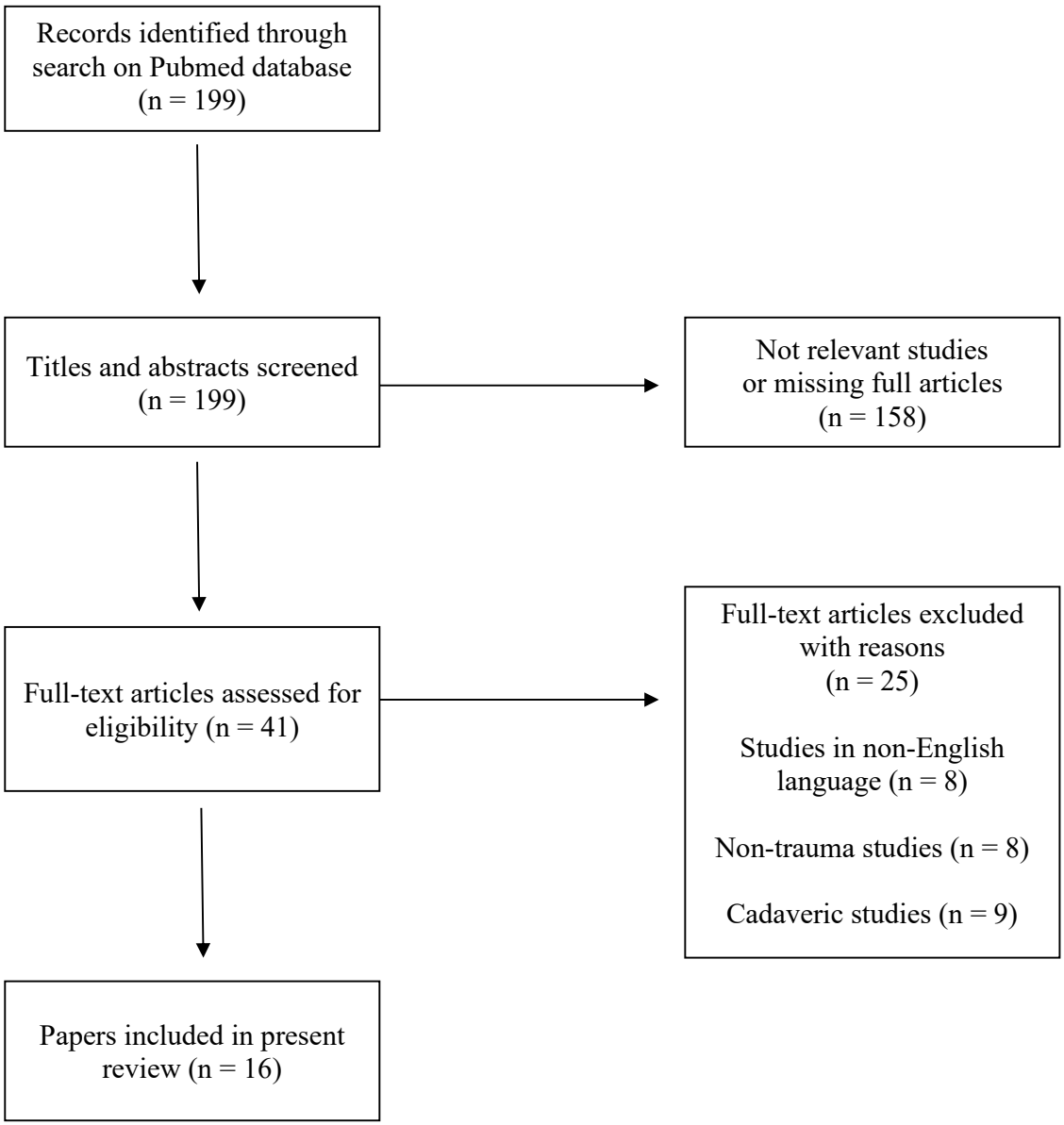
Figure 1. Flowchart



Frankel C (n = 2) and Frankel D (n = 6). Patients underwent posterior stabilization with rod-screw systems (n = 3), plate-screw fixation (n = 25) and combined rods and screws at the thoracic level linked to plate-screw at the cervical level (n = 2). After a mean follow-up of 18 months, reductions were satisfactory in 27 patients, while bony fusion was observed in 100% of the patients on CT scans. Among the 14 patients with partial lesions, 10 patients experienced complete or partial neurological recovery. None of the patients, initially classified as Frankel A recovered neurological function. Authors suggested plate-screw fusion in fractures that do not require fusion beyond T2, whereas rod-screw systems are preferred for superior thoracic

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injuries. Complete SCIs resulted in increased mortality of the operated patients [23].

Case reports

Shah and Rasjshekhar reported a case of a 40-year-old man with a traumatic total spondyloptosis at C7-T1 level, with impaired motion and sensation at all four limbs. The patient underwent ventral decompression and uninstrumented in situ fusion, with a good neurologic outcome [24]. An old study by Pick and Segal reported a case of a 46-year old man with a C7-T1 dislocation treated with surgical stabilization. Patient was permitted to ambulate immediately after surgery [25]. The case of a 70-year-old man with an unstable C7-T1 dislocation was reported by Alsofyani et al. Clinical examination revealed parethesia at C7 and C8 dermatomes bilaterally. The patient underwent anterior cervical discectomy and fusion of C6-T2. At one-year follow-up, x-rays showed bony fusion at C7-T1 level and the patient had no major disability [26]. Another case of C7 on T1 traumatic spondyloptosis in a 60-year-old man with initial bilateral upper extremities paresthesias was reported by Nguyen et al. The patient was subjected to posterior C6-T1 decompression, bilateral C7 facetectomies, C4 to T2 posterior fixation and C7-T1 anterior fixation. At 6 months follow-up, his motor and sensory examination was normal, with a slight paresis of vocal cords [27]. Kim et al reported two cases of traumatic C7-T1 dislocation with tetraparesis treated successfully with single posterior approach and short segment fusion, with the use of cervical pedicle screws. Authors observed improvement of clinical condition [28]. The combined posterior-anterior stabilization was favored by another study by Schmidt-Rohlfing et al, who reported a case of 36-year-old patient who sustained a unilateral fracture-dislocation C7-T1 involving all three columns. The patient was initially treated with posterior fixation and the, at second operation, underwent anterior C7-T1 fusion with a tricortical bone graft and instrumentation [29].

The case of a 41-year old woman with a C7-T1 fracture-dislocation was published by Kyrylenko et al. After anterior plating and interbody C6-T1 arthrodesis with iliac crest bone graft, the patient survived with no neurological impairment [30]. A similar case was reported by Acicbas et al, where a 42-year-old man sustained a total traumatic C7-T1 spondyloptosis after a motor vehicle accident. The patient was initially treated with a C7-T1 discectomy and anterior fusion with a peek cage and allografts and a titanium plate. After 3 days, the patient underwent posterior C4-T3 stabilization with C4-C5 lateral mass screws and T2-T3 transpedicular screws and rod constructs. Complete fusion was observed with no neurological deficit [31]. Mata-Gomez et al reported a case of a 33-year old woman with a traumatic C7-T1 spondylolisthesis and spinal cord signal change, 9 months after a motor vehicle accident. The patient underwent spinal fusion with combined anterior and posterior approach. Initially, with a posterior approach, lateral masses screws were placed in C4-C6 and pedicle screws were placed in T2-T3. Then a partial T1 corpectomy and laminectomy was performed. In a second stage, through an anterior approach, authors performed a C7-T1 discectomy and fusion with iliac graft crest and C5-T2 anterior cervical plate. After a follow-up of 18 months, the patient had a complete neurological recovery [32].

Conclusions

Because of its biomechanical characteristics, CTJ is a unique spinal region, with difficult anterior access. The evolution of surgical techniques and hardware has facilitated the approach and the instrumentation of the CTJ, allowing for low profile, rigid fixation. Complications of operations around the CTJ are frequent and the associated morbidity is significant. Appropriate training along with meticulous preoperative planning, surgical technique and postoperative care are essential for the prevention of these complications. However, optimal surgical procedure has not yet been clarified. More high-quality studies are needed to fully elucidate the best fusion method and approach in order to maximize the benefit for the treatment of these patients.

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The Management of Neuropathic Pain and the Physiotherapeutic Rehabilitation of Patients with Chronic Post-Herpetic Neuralgia

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ABSTRACT

Post-herpetic neuralgia (PHN) is a quite common chronic painful condition occurring as a direct complication of herpes zoster infection. PHN is triggered when the patient is infected with the varicella zoster virus (VZV). Patients with PHN often experience multiple types of pain such as burning pain, paroxysmal pain, aching, hyperalgesia and allodynia over a long period of time. The aim of this review was to evaluate how modern medicine confronts PHN, which types of medications can more efficiently relieve patients' symptoms, how physical therapy can provide the necessary tools for analgesia and prevention, and what other types of physical rehabilitation can be used to integrate those people back to a more painless and sustainable reality. This review was based on articles found on different online databases such as Google scholar and PubMed using keywords as: post-herpetic neuralgia; medicament; neuropathic pain; physiotherapy; TENS; LLLT; rehabilitation; pain relief. Patients suffering from constant neuropathic pain have the right to live with dignity and rejoice. Different medications can be quite helpful and physical therapy can work as a tool for prevention and management of neuropathic pain.

Key Words: post-herpetic neuralgia, medicament, physiotherapy, neuropathic pain, rehabilitation.

Introduction

Post-herpetic neuralgia (PHN) is a neuropathic pain syndrome which produces persisting pain over a long period of time (few weeks to years) after the development of herpes zoster (HZ) rash [1]. One specific characteristic of PHN is that it is age related [2]. The incidence of PHN in patients infected with herpes zoster seems to increase rapidly over the age of 50 [3]. Indeed, the frequency and seriousness of PHN is increased in elderly patients with acute HZ infections, manifesting in 20% of patients between 60 and 65 years old and in more than 30% of patients over 80 years old [4]. Patients with PHN have a decreased quality of life and cannot participate in daily activities, which affects them on a physical, psychological, and social level, as they feel unable to function properly [5].

Skin infection with herpes zoster leads to a rapid production of varicella zoster virus (VZV) specific T-cells, while the production of interferon A promotes the resolution of the infection. Lesions are cre-

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ated within a certain dermatome. Dermatomes commonly infected are thoracic (53%), cervical (20%), trigeminal (15%) including ophthalmic, and lumbosacral (11%) [6]. The HZ rash is usually accompanied by pain and dysesthesia. The rash evolves rapidly to clear vesicles similar to the original chickenpox lesions. Those kinds of vesicles are quite visible to the naked eye. After 2 to 3 days, pustules form, ulcerate, and eventually scab over. Scabs fall off in a couple of weeks and scarring settles [7]. The PHN type of pain can be steady, spontaneous, throbbing or burning, constant or intermittent, and can be sharp or shooting. Allodynia is another common feature of PHN [1].

The goal of therapists is to determine which type of pain the patient is experiencing and find the suitable type of treatment. The most common type of treatment in order to manage PHN is oral or topical medications. However, there are other modalities such as physical therapy alone or in combination with medications which give promising results.

The aim of this study was to review the use of different medications and physiotherapy protocols in the treatment and rehabilitation of patients suffering from PHN. For this reason, a review of the current literature was conducted using the online Pubmed and Google Scholar databases and following the PRISMA Guidelines. Article titles were searched by using the following keywords: post-herpetic neuralgia; medicament; neuropathic pain; physiotherapy; TENS; LLLT; rehabilitation; pain relief; treatment. Inclusion criteria in the review were: studies that evaluated the treatment and rehabilitation of patients with PHN, published after 2000 in English language. Studies in other than English language, animal studies, reviews, case reports, and clinical protocols were excluded from the study. The initial search resulted in 93 articles. After reviewing titles and abstracts, 15 studies were rejected as irrelevant. Of the remaining 78 studies evaluated, 49 were rejected for not meeting the study criteria. Eventually, 29 full text articles were assessed for eligibility. Out of those 9 were excluded for being irrelevant, giving insignificant results or evaluating vaccination techniques for early prevention. Finally, 20 randomized controlled trials were included in this review (Table 1).

Discussion

Pain management with Medication

Prescription medicine has always been the most certified way to treat painful conditions. Post-herpetic neuralgia is one of those conditions and is mostly treated by drugs. Tricyclic antidepressants (TCAs), pregabalin, and gabapentin are generally the drugs that are recommended for the treatment of PHN [1]. Treating patients with a daily dose of 1800mg of Gastroretentive Gabapentin, is a well-tolerated and effective way for treating PHN, in patients of all age groups [8], [9]. In addition, pain reduction has been observed with the use of a topical Xylocaine pump spray, when applied over the painful region in patients who suffer from PHN, showing superior results when compared to a placebo pump spray [10]. The use of liquid nitrogen (LN spray) is another form of pain reduction treatment called cryoanalgesia. In a recent study, it was observed that the application of LN spray on the affected dermatome for 30 seconds produces good or excellent results in terms of pain reduction in 94% of patients, right before the sixth session [11]. Furthermore, it has been shown that the therapy with a combination of amitriptyline, a tricyclic antidepressant, and LN spray is an alternative which can easily replace a combined therapy of gabapentin and amitriptyline, producing the same results in patients with PHN [12].

A recent clinical trial conducted in Asian patients evaluated a specific drug called mirogabalin for its safety and efficacy as a long-term medication in patients with PHN. This study elucidated the safety and the stable pain relief of a long-term flexible dosage of 10 or 15mg mirogabalin given twice daily, for 52 weeks in patients with PHN [13]. In another study, NGX-4010, a high concentration capsaicin dermal patch (capsaicin 640 mg/cm2), was used as topical treatment applied for 1 hour in PHN patients. Patients were able to receive up to 3 treatments with a break of 12 weeks between each treatment. NPRS was used as a benchmark to determine pain fluctuations during the study. Pain decreased by 33.8% during weeks 2 to 12 in the treatment group. The authors concluded that their approach can reduce PHN pain and that this outcome can be maintained for up to 1 year [14].

Noninvasive Therapies

There can be different approaches when it comes to

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pain management in patients with PHN. Some of those include Spinal Cord Stimulation, Scrambler therapy and Repetitive Transcranial Magnetic Stimulation (rTMS). In a recent study, it was shown that Spinal Cord Stimulation (SCS) and Pulsed radiofrequency (PRF) can effectively relieve PHN symptoms even though PRF was used on the controlled group. NRS-11 was used to determine pain fluctuations and in the end pain relief ranged from 37% to 71% [15].

A study published in 2012, showed that Scrambler therapy relieves chronic neuropathic pain better than alternative drug therapy even in PHN patients [16]. In 2013, another specific study focused only on whether Scrambler therapy is efficient on PHN patients. The authors concluded that Scrambler therapy given in 30 minutes sessions for 10 days has a promising effect on relieving PHN symptoms. There were no side effects and pain reduction was more than twice compared to any other conservative approach [17].

Moreover, in another recent study, the authors concluded that 10 sessions of rTMS targeted over the painful region on primary motor cortex, with a stimulation of 300 pulses per 5sec (f=10 Hz) with a 3sec interval between each train, were efficient in reducing pain acting complementary to medical treatment. VAS has been used to determine pain fluctuations [18]. A similar study to the previous one, with a related protocol, concluded that both 10-Hz rTMS and 5Hz rTMS are safe, effective and can partake in relieving pain in patients with PHN [19].

Physical therapy

Physiotherapy can a be a part of the rehabilitation program when it comes to PHN patients. Physiotherapeutic approaches like the use of TENS (transcutaneous electrical nerve stimulation) or LLLT (Low level laser therapy) can be quite promising.

Transcutaneous Electrical Nerve stimulation

TENS is a technique used to relieve pain by stimulating nerves with electrical currents applied through patches attached to the skin. TENS is also used as a prevention tool against PHN. The majority of patients with PHN that received TENS therapy as an analgesic, showed a significant drop to their pain scores when compared to other patients that received a sham device [20]. In terms of prevention, a study published in 2012 showed that among the treatment groups, patients who were treated only with TENS did not develop PHN. On the other hand, 28.6% of the patients who received only antiviral drugs developed PHN [21]. The authors of another similar study published in 2013, based on the fact that a group of patients with acute herpes zoster infection who received TENS didn't express PHN symptoms, suggested that TENS was superior to antiviral drug therapy on preventing PHN [22]. In another study evaluating combined treatments, TENS in combination with a local injection of cobalamin produced a significant analgesic effect in a group of patients with PHN. Indeed, 28 of 30 patients in this group experienced 30% or greater pain reduction while patients in other groups receiving different therapies showed inferior results [23].

Low level laser therapy (LLLT)

Low level laser therapy (LLLT) is a therapy using a low intensity laser machine. The laser light triggers a biochemical reaction within the cell, which leads to chemical changes. It is used as anti-inflammatory and analgesic therapy. In a recent study, published in 2016, LLLT was used as a means of prevention against PHN. The study showed that the application of LLLT within the first five days of HZ symptoms reduces the chances of developing PHN [24]. Additionally, in another study, the use of 830 nm diode laser for 20 minutes per treatment (Group A), produced a significant reduction in pain score by 80% in the first four sessions, in contrast to the control group (Group B) that only showed 10% reduction [25].

C.A.M Therapy (Complementary and Alternative Medicine)

Complementary and Alternative Medicine is a type of rehabilitation approach that is not a part of standard medical care. Techniques like acupuncture, which can be applied by a physical therapist, and TCM (Traditional Chinese medicine) are often used for pain relief. In a recent study, the use of a CAM protocol led to a significant reduction of chronic post-herpetic neuralgia pain within the first 3 weeks of treatment. The CAM therapies used were acupuncture, TCM herbs, neural therapy (1% procaine injection), cupping and

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bleeding. Improvements lasted for up to two years [26]. Furthermore, a recent study has shown that a treatment group, receiving as therapy a combination of acupuncture and electroacupuncture for 30 mins per session, 5 times a week for one month, had better results in terms of pain reduction compared to the control group, which was treated with acupuncture and moxibustion. (VAS and HAMA scales were measured and compared between the two groups) [27].

Conclusions

PHN is a chronic painful condition that needs to be treated accordingly. Patients suffering from constant neuropathic pain have the right to live again with dignity and rejoice. Different medications can be quite helpful and physical therapy can work as a tool for prevention and management of neuropathic pain. Physical therapy has an extensive field and should be applied according to the patient's needs.

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Strategies for treatment of pain, psychological deficits and quality of life deficits in people with Spinal Cord Injury

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ABSTRACT

Chronic pain is a usual phenomenon in persons living with spinal cord injury (SCI). Populations with spinal cord injury (SCI) have an increased risk of depression, anxiety, pain, and poorer quality of life (QoL). This systematic review aimed to identify interventional research regarding the care provided for people with SCI during rehabilitation and synthesize the evidence of the effects and characteristics of these studies regarding their effects on depression, anxiety, pain, and poorer quality of life (QoL). Databases (Cochrane, MEDLINE, Embase, PsycINFO) were reviewed from the 1st October 2020 to January 2021. Twelve papers met the inclusion criteria, and demonstrated a range of results of interventions delivered individually, in a group format, in person, and online. Only seven studies reported significant reductions in pain-related outcomes (with moderate effect sizes), with the remaining studies (n = 5) demonstrating no change. Four studies described reductions in depressive symptoms and five reported reductions in anxiety. Quality of life was assessed in six studies although in only four studies significant gains were found. Study quality ranged from high to low/weak. This review found promising evidence that some approaches for people with SCI can improve their pain relief and psychosocial adaptation (pain management program, cognitive Behavioral therapy, mindfulness, exercise, psychological education, transcranial direct current stimulation). Although significant methodological limitations weakened study findings. Additionally, studies were conducted in only a few developed countries with subgroups of patients having specific illness characteristics or severity, therefore their generalizability to the wider SCI population is uncertain. Consequently, future research should adopt more robust study designs to test interventions targeting pain relief and the psychological well-being of patients with SCI with different socio-cultural backgrounds and psychological adjustment conditions in the early stages of rehabilitation.

Key Words: Spinal cord injury; Rehabilitation; Pain; Quality of life; Psychological adjustment; Mental health

Spinal cord injury (SCI) leads to sensory motor deficits that are partial or complete (1). Populations with SCI usually face secondary complications such as psychological complications at an increased rate then the general population (a 22,2% of this population is affected by depression and anxiety) (2) in addition to a

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downsized Quality of life (3). Research also supports that there is a a mutually reinforcing relationship between chronic pain and depression in this population (4). In this population besides the secondary complications the primary issue that affects this group of patients is chronic pain, that also appears to be resilient to pharmacological treatment (5).

Research has begun to investigate the role of interventions (physical and psychological) in improving pain and psychosocial outcomes after spinal cord injury. However, the benefits and side effects of non-pharmacological treatments remain unclear (6). Studies have investigated the effects of non-pharmacological interventions in the treatment of chronic pain; however, they show deficiencies in their design. A particular problem is the use of inappropriate control interventions, such as waiting lists. It has been shown that in direct comparisons, placebo interventions tend to be superior to untreated or waiting list control interventions, especially for related to pain variables (7).

At present, it is therefore difficult to make decisions regarding the use of non-pharmacological treatments for chronic pain in people with SCI. Therefore, the objectives of this systematic review were:

• To synthesize and critically evaluate the available quantitative and qualitative data on the effects of interventions on pain and the results related to pain, depression, stress and quality of life in people with SCI.

• Make specific recommendations for future research based on existing knowledge of the present literature.

Methods

Studies included participants living with Spinal Cord Injury, regardless of age, gender, and severity of disability. Both traumatic and non-traumatic injuries were included. Studies involving participants with other conditions were included if the results from the Spinal Cord Injury subgroup were presented separately from the other groups. Also included were studies in which interventions were performed within a hospital setting or health facilities.

Non-pharmacological study interventions were defined as experimental treatments that did not involve medication or any other active substance. Eligible treatments included surgery, exercise, acupuncture, massage, joint mobilization, relaxation training, heat therapy (hot or cold application), static magnetic field therapy, brain stimulation, and psychological or behavioral therapies, as well as psychosocial (e.g. therapy, skills training, psychological education, supportive intervention, counseling, counseling, visual imaging, hypnotic therapy). However, studies on other interventions, such as the use of durable equipment, were only considered if the focus was on treating people with chronic pain.

While studies that included single or combined psychosocial approaches such as Cognitive Behavioral Therapy, skills training, psychological training, supportive interventions or counseling were also included. These psychosocial interventions were carried out within the usual care framework for people with SCI. where also pharmacological and medical treatments may be provided.

This systematic review includes other interventions such as stress reduction techniques through mindfulness, meditation, yoga, conscious mobility, awareness in daily life, and breathing techniques that are not included as documented psychological therapies or, as well as psychosocial approaches. Interventions involving consciousness as part or all of the intervention were included in this review.

Control interventions included active pharmacological or non-pharmacological treatments, placebo interventions or waiting list groups.

Results

Twelve papers met the inclusion criteria (8-20), and demonstrated a range of results of interventions delivered individually, in a group format, in person, and online. Only seven studies reported significant reductions in pain-related outcomes (with moderate effect sizes), with the remaining studies (n = 5) demonstrating no change. Four studies described reductions in depressive symptoms and five reported reductions in anxiety. Quality of life was assessed in six studies although in only four studies significant gains were found. Study quality ranged from high to low/weak.

The heterogeneity and methodological flaws of the studies would not allow the generalizability of the findings and their effectiveness. Nevertheless, ten of those examined the depression symptoms, ten of them measured stress, nine studies examined pain while six

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studies examined quality of life.

A study found transcranial direct current stimulation (tDCS) to be superior to a fake intervention but the overall evidence shows a vague positive result on chronic pain in patients with SCI. Exercise as an intervention for chronic pain was beneficial but still had methodological flaws (blinding and randomising). Moreover, studies on chronic pain which utilized control groups without any therapy or waiting list groups were found to be problematic because they would have different outcomes even compared with placebo interventions.

In psychosocial interventions alone or with mindfulness, focusing on pain reduction or quality of life, demonstrated short term outcomes in comparison with other interventions (exercise) and they were less effective. Nevertheless, the outcomes were not clear because of the heterogeneity of the different approaches and assessment tools used in every study and it was difficult to explain the underlying therapeutic mechanism (if any). Unexpectedly, a cognitive behavioral therapy was generally adopted from most researchers utilizing psychosocial interventions and it might be the reason for these studies to have beneficial outcomes. The findings of the present review showed that there is need for further research in order to positively support the use of mindfulness in favor of other interventions.

Despite the firm application of literature review methods and the methodologic assessment as well, there are certain limitations to be taken into consideration. There is a chance that during literature research, selection bias was introduced due to not selected studies which should be included, mainly because they were not published in peer review issues. Another limitation was the presence of only one reviewer.

Conclusions

Overall, this review found promising evidence that some approaches for people with SCI can improve their pain relief and psychosocial adaptation (pain management program, Cognitive Behavioral Therapy, mindfulness, exercise, psychological education, transcranial direct current stimulation). Nevertheless, significant methodological limitations weakened study findings. Additionally, studies were conducted only in a few developed countries with subgroups of patients having specific illness characteristics or severity, therefore their generalizability to the wider SCI population is uncertain. Consequently, future research should adopt more robust study designs to test interventions targeting pain relief and the psychological well-being of patients with SCI with different socio-cultural, economic, clinical backgrounds and psychological adjustment conditions in the early stages of rehabilitation. Such programs should be evidence-based, cost effective and with a standardized protocol in order for them to be easily applied into the inpatient and outpatient rehabilitation schemes by health professionals.

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