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ACTA ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

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- Osteoimmunology of Fracture Healing: A Brief Review on the Immune Systems' Cellular Milieu Role in Bone Injury
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or

Papaioannou NA, Triantafyllopoulos IK, Khaldi L, et al. Effect of calcitonin in early and late stages of experimentally induced osteoarthritis. A histomorphometric study. *Osteoarthritis Cartilage* 2007; 15(4): 386-95.

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Provision of medical care to the 1821 Hellenic Revolution Fighters

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ABSTRACT

The fight to free the enslaved by the Turks Greeks in the 1821 Hellenic Revolution was not only in battlefields restricted. The contribution of medical personnel to the wounded was equally invaluable leading to the final victory. Access to medical treatment proved extremely difficult. Existing public health conditions along the Turkish rule could be politely deemed from miserable up to unacceptable. Many young scientists, students or graduates from European medical schools preferred to remain in the attractive western world. Few of them motivated by their genuine patriotism returned to their homeland in order to offer their knowledge and skills. Practical doctors and to some extent doctors staffing the tactical army, mainly foreigners supporting Hellenic nation into its struggle to liberate itself (Philhellenes), carried out the duty for medical care in battlefields. Of course, during this destruction empiric healers and charlatans grabbed the opportunity to declare their exceptional healing skills!

KEY WORDS: Hellenic Revolution 1821, medical care, public health, empirical doctors, Philhellenism.

Introduction

Hellenic Revolution in year 1821 came as the inevitable effect of many factors' confluence. Historians never undermined the role of coincidence that enhanced the rise for liberation of the enslaved Hellenes. Gradual dissolution of Ottoman Empire had already started with the insurrection of Ali Pasha. In the interim, the scripts of Adamantios Korais and the passionate preaching of Rigas Phereos expressed the New Hellenic Enlightenment. At this atmosphere, the impact of Kosmas Aetolos' teaching was awakening the common conscience. At the same time, induction in the Society of Friends ("Philiki Eteria"), and the illusion for support by the czarist Russia, created hope for redemption from the long-standing Turkish rule. All these like a catalyst and through lots of mystery led to the idea of the birth of the Hellenic Nation, with distinct po-

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litical existence and definitely connected with Ancient Greece.

Despite all that, the reconstitution of Ottoman power, combined with Greek civil unrest, put the outcome of the Revolution in doubt even from its beginning. Austrian chancellor Klemens von Metternich was furiously attacking Greek Revolution at every instance. However, when Ibrahim's expedition failed due to combined effort of all Superpowers then Austrian chancellor was forced to change his mind [1,2,3].

In the collective consciousness, the 1821 Hellenic revolution is connected to specific people and events: with Kolokotronis in Dervenakia, with Diakos in Alamana, with Papaflessas in Maniaki and with Karaiskakis who fought and pushed Kioutachi Pasha out of Keratsini. Nevertheless, many historians support that eventually the heart of this fight belonged to the soul of the public and enthusiastic simple people [2,3]. At the same time, Philhellenism in Europe was growing fast especially after the civilian massacre in Chios island (**Fig. 1**). Telling are Victor Hugo's lyrics from the poem "Enthusiasm" which encourage his fellow citizens to fight next to the Greek rebels: "*…for the sacred revenge/ for our Goddess Freedom*".

The research for the causes that led to the eruption of the Hellenic Revolution in 1821 as well as the details who resulted in its final success does not end here. Medical care to fighters, for example, was never systematically approached, as someone would expect. Healthcare demanded combined attempts, which were not self-implied at that time during these bloodiest events. Public health was compromised and set up of any healthcare service was absent. Medical provision was mainly based on empirical practitioners and at a lesser extent on Greek and Philhellenes doctors belonging to the tactical army.

Public Health during the Ottoman rule

Gathering information from valid sources [4,5,6] it would not have been an overstatement that quality of life during the Revolution was clearly outstandingly poor. For the degraded public health condition, someone could blame the fighters who were frequently changing places, congestion in urban areas without any decent healthcare provision (**Fig. 2**), longstanding siege of cities or fortresses and generally the frequent battles, which hindered any plans to improve the health status. And apart of all the above we should add sanitary problems, famine, humidity, special environment of Greek countryside where battles were taking place, as well as various sewage problems.

The first health outbreak after the declaration of the Revolution was noted in Tripoli; it had to do with rash typhus and caused the death of 3,000 people. A typhus epidemic was later on manifested in Nafplio but also in other cities under siege. Main diseases that infested fighters and their families were dysentery, cholera, plague, smallpox and malaria. Taking into account that Medicine's big progress took place in the second half of 19th century, and then, we will able to justify this epidemic spread. Humanity would delay slightly more to reach the time point to recognize pathogens, to produce vaccines and to operate under strict aseptic rules. Louis Pasteur, Robert Koch and Joseph Lister were just born during the Hellenic Revolution.

Fighter's nutrition included mainly bread, wheat cracker and boiled corn. Meat and fish were available rarely. Wine and raki were supplementing their table. The only item that never lacked during the Fight was the olive oil. However, during siege like in Messolonghi, people sustaining the occlusion after the exhaustion of resources were resorting to whatever was amenable to be chewed (**Fig. 3**). In the begging, they were consuming domestic animals like horses, mules, donkeys, camels, dogs and cats and later on mice and animal leathers. At their despair in front of the upcoming death, they even reached the point to eat dead human bodies before disintegration.

We know today from valid sources that the water from wells was constantly contaminated. Dionysios Kokkinos wrote that suitable wells in Argos were exhausted and the minimum remaining water was poisoned by the oxidation of the household items abandoned by the inhabitants with the scope to retrieve them on their return [1]. In the Messolong-

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Figure 1. *"Chios Destruction" by Eugène Delacroix (Louvre Museum).*

Figure 2. *"Karaiskakis Military Camp in New Faliro" by Theodoros Vrizakis (National Art Gallery in Athens).*

hi Nikolaos Kasomoulis wrote that water from the wells was a peculiar mixture of brain, intestine, blood and heads [7]. Despite all this hardship, the Greek courage was never affected. They continued their fight despite being hungry, wounded, ill and exhausted, with perseverance, optimism and belief in the idea of liberation.

Medical scientists during the Revolution

During the Turkish rule, many young people from different areas across the enslaved Greece registered to European universities for studies, especially medicine. They usually chose Padova, Pavia, Pisa and Vienna. Many of these medical graduates gained authority in the Ottoman governmental hierarchy. Alexandros Mavrokordatos and Panagiotis Nikousios achieved to become Great Interpreters. Petros Ipitis organised philhellenic organisations across Europe. Adamantios Korais dedicated big part of his life to the Greek Enlightenment supporting the undoubted principles of education and language. Ioannis Koletis was also involved in politics.

It is remarkable that Rigas Phereos was surrounded and supported by the doctors Ioannis Emmanouil, Nikolaos Polizos, Dimitrios Nikolaides, and Petros Fragos and by the medical students Konstantinos Karakasis, Christophoros Perrevos and George Sakellarios. When due to treason the Austrian discovered Rigas Phereos' revolutionary plans, they arrested Perrevos who was eventually dismissed because Rigas offered a good excuse for him stating that he encountered Perrevos all by chance as he was coming to Trieste to study medicine [8].

Medical doctors were also participating in Philiki Eteria. Many others stood out as great financial donors contributing to the collective liberating fight (Apostolos Arsakis from Epirus, Delaportas from Kefallinia, Sakellarios from Kozani and Flevas from Naousa). Ioannis Kapodistrias, the first Greek governor, was a doctor graduate from Padova.

The only case of a Turkish doctor proving to be a selfless servant of Hippocratic Oath was that of Hasan Ali Kourtalis. He was living with his family in Atalanti working as empirical surgeon. After the Revolution outbreak, he saw his family being slaughtered by those whom will medically treat later on. In Acropolis siege, he treated General Makrigiannis and Odysseus Androutsos as well as many others.

Very few from the medical scientists chose to get actively involved and offer their services to the fighters **(Fig. 4)**. Most of them treated medical conditions. Care for the wounded in the battlefields was based on foreign Philhellenes doctors and mainly on practical or empirical doctors.

Medical Service of Tactical Army

Law reconstituted the tactical army of the inde-

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Figure 3. *"Messolonghi Exodus" by Theodoros Vrizakis (National Art Gallery in Athens).*

Figure 4. *"Death of Markos Botsaris" by Theofilos Chatzimichael (Theofilos Museum in Varia of Mytilene).*

pendent Greek state on 1st April 1822. The first units were the Heavy Infantry Regiment and Battalion of Philhellenes. The first doctors who joined were coming from Germany, Denmark and Switzerland [4,5,8].

An extraordinary case was the one of Heinrich Trieber **(Fig. 5)**. He was born in Meiningen of Germany in 1796, studied medicine in the Universities of Jena, Erlangen and Würzburg and was specialized in Surgery in Paris. Most information is obtained by his personal diary, which covers the timeframe from January 1822 when he first put his foot in Greece up to April 1828 when he undertook the management of the Military Hospital of Acronafplia. He took part in many battles and other military missions. He was given the unpleasant duty to perform Lord Byron's autopsy and some years later to write the coroner's report for the murdered Ioannis Kapodistrias [9].

Heinrich Trieber took part in planning of the first Military Hospital and of the Municipal Hospital. He founded the Military Pharmacy and became assistant professor of Surgery in the University of Athens. In 1842, he was appointed as King Otto's personal doctor. He introduced in 1847 anaesthesia with ether in Surgery, some months after its first application by William T.G. Morton in Massachusetts on 16th October 1846. In the 1854 cholera pandemic of Athens, he was proactive treating patients at his own risk. Eventually he became sick but managed to recover. When in 1864 he retired, grateful motherland awarded this humble scientist with many honours and prizes. He died in 1882 at the age of 86.

Medical graduates were coming to rebelled Greece from all over the world to offer scientific knowledge and foremost their own life. Samuel Gridley Howe, a graduate of Harvard University, left Boston led by romantic and philhellenic feelings and managed to reach Greece, where exhausted from his long journey wore his "foustanela" (Greek traditional skirt worn by males) and was appointed as surgeon in Mavrokordatos' army. He contributed to the setup of a temporary hospital and of a transport service for the wounded and he soon followed a small military squad where, as one of his fellows revealed, *"He was becoming a surgeon when the battle was over"*. After his return to USA, Howe founded a prototype foundation for the blinds, the renowned *Perkins Institution*. Much later in March 1867, after the Cretan revolution, he transferred money and food for the refugees and citizens of Crete [4,5].

At the same time, Switzerland exhibited true acts

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Figure 5. *"Heinrich Trieber". Oil on canvas (National Historic Museum of Athens).*

of philhellenism. Johann Jakob Meyer published the *"Hellenic Chronicles"* and lost his life in the heroic Messolonghi exodus. Henri Amsler died from typhus in Milos Island. Henri Dumont fought during the Revolution. Louis-André Gosse with his multifaceted medical, political and editorial activity was highlighted as representative of public life in his country and as a crusader of Swiss philhellenism. He co-operated with banker Jean-Gabriel Eynard and organized money and resource transfers to rebel Greeks. He was assigned as general supply chain commissioner of the naval fleet and Archipelagos' tax inspector. He participated in philhellenic committees for supply distribution. Moreover, he hospitalised the lethally wounded Karaiskakis **(Fig. 6)**. He submitted report for the function of the first hospital in Nafplio to Kapodistrias [4.5].

After March 1829, Greeks were appointed as doctors of the tactical army apart from the foreigners **(Fig. 7)**. Indicative examples are Stylianos Emilios from Lesvos, Chronias Drosinos from Ampelakia, Stephanos Kritis and Antonios Polilas from Corfu.

Figure 6. *"The battle of Athens and the lethal wound of Karaiskakis" by Alexandros Isaias. Oil on canvas (National Historic Museum of Athens).*

The practical doctors

Historians unanimously agree that practical doctors were the ones who bared the biggest load of fighters' medical care. They were skilful in reducing fractures and dislocations, in cleaning wounds and in performing minor operations. Transfer of knowledge and experience of practical medicine was passed from father to son like a family tradition. However, relevant schools were operating in Athens, Karpenisi, Sparta, Corfu and Chios. Panagiotis Giatrakos founded a medicopharmaceutical school in Mistras prior to Revolution outbreak. He had studied medicine in Italy for a short period, was member of Philiki Eteria and captain of a military unit. Before the Revolution, he had received 300 boxes full of drugs and surgical instruments. Five younger brothers of Panagiotis Giatrakos had also attended the Mistras School.

In relevant sources, we can find numerous practical doctors who contributed at the same timeframe. Most renowned is a woman, Helen Mavrovouniotis, the wife of captain Vassos Mavrovouniotis. In practical doctors also the name of François Pouqueville, French consul in Greece, is included [4,5].

When the Revolution was declared, there were no administrative measures and there were shortages of supplies and drugs. The term "Organized Healthcare Service" was completely unknown. Available drugs for the practical doctors were merely some herbs. Wounds were dressed with pieces of fabric and haemostasis was accomplished with

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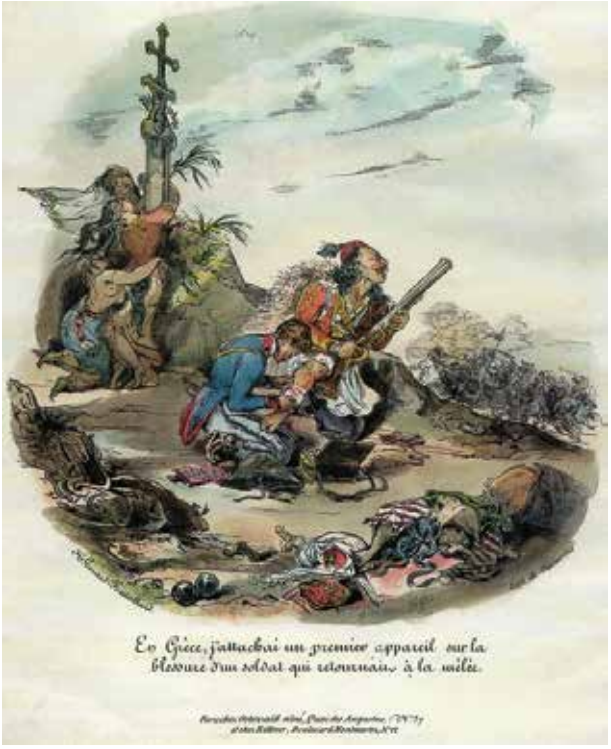

Figure 7. *"French military doctor treating the wound of a Greek Fighter". Painted engraving (National Historic Museum of Athens).*

Figure 8. *"The death of Lambros Tzavellas" by Donato Francesco de Vivo. Oil on canvas (National Art Gallery and Alexandros Soutzos Museum. Nafplio Branch).*

burning steel. They were retting the external side of the dressings with ointment made up from soap and raki. Inside the wounds, they were usually applying ointment from egg albumen and oil. For fractures, they were using improvised splints made up from wood or paperboard **(Fig. 8)**.

In his autobiography, General Makrigiannis describes that they were using big ants to bite the wound edges and when they were ready to close their jaws, the fighters were beheading them forming with this way a strong suture [10]. Photakos mentions that they were using hot butter against oedema and bruises [11].

Drugs, which practical doctors trusted, were droges (extraction of crude drug), some substances or items containing balsam, elixir and laudanum, all brought from Konstantinoupolis, Smyrna, Eptanisa and Trieste. They were also using opium poppy as sleeping pill, saltwater against lower limb swelling, and tatary buckwheat seeds as an emetic [12].

Practical doctors were able to examine and clean wounds thoroughly, to remove the responsible bullets and to isolate osseous fragments or big bone butterflies. Lightly wounded received care on site in battlefields **(Fig. 9)**. Heavier wounded were transferred to nearby monasteries (Oblou Monastery in Achaia and Zoodochos Pigi Velanidias Monastery in Messenia) or to substandard hospitals.

Apart from the known sword and the scimitar, a sword with curved edge-*"giatagani"* **(Fig. 10)**, weapons used by the two fighting parts were the pistol (short-barrel gun 58mm-*"pistola"*), the trombone (gun with flat barrel and flint mechanism releasing many pellets together at once) and the musket (front-loading riffle with long barrel and contemplation-*"kariofilli"*). These guns did not have long range and the causing damage was variable depending on the distance. Fighters were wishing each other *"kalo voli"* (Good shot), implying a quick, painless and heroic death [4,7].

Fake doctors were also performing medical duties and were prescribing drugs parallel to the practical doctors. They were mostly known as charlatans or *"kombogiannites"*. They were administering peculiar substances of unknown origin and their advice was usually complex and difficult to apply [4,6,12]. They tended to praise their supposed own therapeutic skills to a usually freaking extent but their interest was mainly the financial profit.

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Figure 9. *"Wounded Greek officer outside the walls of a captures city" by Jean Claude Bonnefond. Oil painting in tarpaulin*

Figure 10. *"The Combat of the Giaour and Hassan" painting by Eugène Delacroix. Oil on canvas (Art Institute of Chicago).*

Epilogue

According to Professor of History of the University of Konstantinoupolis Esra Özsüer: "*The proposed opinion in Turkish historic teaching is that revolutions across Balkans were the result of the ungratefulness of Greeks and other Balkan nations who were peacefully living under the Ottoman bliss*" [13]. Therefore, it is easy to recognize nowadays the significance of the struggle in order to breathe as free Hellenic citizens without forgetting dividing practices who led to dead ends.

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Osteoimmunology of Fracture Healing: A Brief Review on the Immune Systems' Cellular Milieu Role in Bone Injury

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ABSTRACT

Bone fracture healing is the most common medical treatment in the usual clinical practice. Bone has the unique property for self-healing, which is in addition to the ability of not forming a scar. Following fracture, a chain of events takes place, which include the activation of healing processes in both the cellular and tissue level. These events, lead to a full bridging of the gap between the two bone-ends of the fracture. In that process the immune system is active and the immune cells are known to play a significant role. The process of fracture healing can be divided in three main steps; these are sequential in nature and independent. The first phase includes the inflammation phase, which involves the acute activation of the immune system, the second phase includes the repair phase, which involves the recruitment of mesenchymal progenitor cells differentiating to chondrocytes and the final phase involves remodeling, where osteocytes are recruited in order to form the new bone. In conclusion, immunity serves as the initial responder at the skeletal damaged site, restores the vasculature, and initiates cascades of signals to recruit cells to carry out the repair processes. Therefore, it is believed that the immune system can be considered as a promising therapeutic target for bone fracture healing.

KEY WORDS: Fracture Healing, Immune System, Bone Fracture, Bone Healing, Immune Cells

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Introduction

Bone as a tissue has the unique ability of healing itself without forming a scar (1). However it is reported that 5%-10% of the fractures result to permanent failure of healing, yearly, a rate that increases with certain comorbidities and aging (2). There is a need for the regulation of skeletal homeostasis that is controlled not only by the musculoskeletal system but by the combination of multiple biological systems as well (2). There are various "regulatory molecules" that both, the skeletal and the immune systems, share such as cytokines and signaling molecules, and thus the immune system is in close relation with the bone system (3). This interaction between osteo-cells and parts of the immune system, which are known for their role in bone repair, retains a great research interest from scientists and clinical practitioners (4), as it is known that bone fracture healing is tightly in cooperation and under the strong regulation of the immune system (5).

As the bone marrow is the main site of hematopoiesis, it hosts Hematopoietic Stem Cells (HSCs), as well as mature immune cells, including B-cells, neutrophils, macrophages and T cells (6). Although previously neglected, the bone and the immune system share the same microenvironment, where they interact consisting of the "osteoimmune system". This system, involves all bone marrow cells. For historical purposes, the discipline of "osteoimmunology" was developed in order to investigate the underlying molecular mechanisms of bone healing linked to inflammatory processes. An older work of Horton *et al*. (1972) referred to the possible interactions between the skeletal system and immune cells, after studying cases of periodontitis (7), where immune cells stimulated by bacterial antigens procured the production of "osteoclast activating agents" (7). Much later on, the term "osteoimmunology" was coined by Arron & Choi (2000), which emphasized the T-cell-mediated regulation of osteoclastogenesis in the context of arthritis autoimmunity mechanisms (8, 9). This was one of the first studies concerning the correlation between osteocytes and the immune system, in terms of the autoimmunity machinery. Thus, immune/skeletal communication is a "round trip", where the key players are the osteoblasts/osteoclasts and the cells of the hematopoietic system. At the same time, bone has been shown to play a role both in the normal development of the immune system through the Hematopoietic Stem Cells (HSCs) in the bone marrow, as well as in acquired immunity. It is also known that memory T- and B-cells always return to the bone marrow. One of the key-molecules that are known to play a role is RANKL, whose part in osteoimmunology is still under investigation (10), while its role seems to extend beyond the bone. For example, its immunohistochemical expression has been studied in association with RANK and OPG in gingival tissues where they appear to play a major role in periodontal bone loss (11, 12).

There are three sequential phases that consist the process of fracture healing which however remain independent. These phases are: "*inflammation*, *repair* and *remodeling*". The triggered local inflammatory response ignites the fracture healing process that leads to the remodeling and repair phases (13). When a bone fracture occurs, a hematoma is formed because of the ruptured vasculature, embedded in the proximal bone and the bone marrow. In this hematoma, various immune cells infiltrate, including the complete niche of white blood cells (14). These cells, it is believed that they are activated by molecules derived by the injured tissues, and after activation the immune cells produce pro-inflammatory cytokines at the injury site, in order to induce acute inflammation (3). After the inflammatory phase, mesenchymal progenitor cells assimilate around the bone lesion, which in turn they differentiate to chondrocytes. The differentiated chondrocytes synthesize cartilage forming a matrix, which is known as "*callus*" and at that phase is soft. The soft "*callus*" bridges the injured bone fragments and afterwards this soft callus is replaced by a hard "*callus*", which also consists of bone tissue. This hard "*callus*" undergoes additional remodeling by activated osteoclasts and osteoblasts, which act further for the purpose of restoring the original morphology and function of the bone without any scar formation (3, 14-16).

Control of Fracture Healing

Repair and restructuring of bone injuries (fractures,

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lesions) are under the close surveillance of the immunological machinery. The immune system is considered to be crucial for this healing process because in the sequence of the events taking place, first inflammatory mechanisms are triggered, followed by bone healing. From observations in patients under immunosuppressive treatment, it became apparent that bone injury and fracture manifested delays in the healing process and higher frequency of nonunion. This conclusion was further supported by similar observations in HIV patients (3, 17-20).

Fracture healing consists of anabolic and catabolic phases during which both intrinsic and modulatory immune functions are essential (14). The first responses to bone injury include the cell-mediated immunological response, which causes the initial inflammation and thereafter followed by the removal of necrotic tissue, the induction of angiogenesis and the initiation of repair (21-23). While the inflammation response lasts for a short time, the immunological response extends at longer time intervals, ranging from the first response to later stages of bone healing (1). The immune cells participating in the process are thought to be activated by molecular mechanisms that is signaling molecules excreted at the injury site, which in turn release pro-inflammatory cytokines eliciting acute inflammation (3). The necessary first steps during the inflammation stages include clotting, tissue granulation, and cell recruitment, which depend on the coordination of various immune cells. Hematopoietic cells seem to direct mesenchymal cell differentiation and activity throughout the different phases of this procedure (1).

However, a controversial finding, suggests that a bone fracture leads to immunological suppression (probably due to the induction of the stress mechanisms induced). Immune suppression is believed to take place due to local activation and increase of induced T-regulatory (iT_{REG}) cells, which suppress active intrinsic immune responses within the fracture "*callus*" (24, 25). Several studies have highlighted the role of mesenchymal stem cells, which convey immune tolerance during the early stages of "endochondral bone formation" and provide a kind of "sheltering" for the developing tissues. This is known to take place by the suppression of T-cell alloproliferation during stem-cell recruitment and cartilage formation (14, 25). However, if inflammation insists or remains unresolved, like when there is a bacterial infection at the fracture site, healing is possible to fail (26).

Immune Cells function and origin

Platelets

Platelets have been shown to have a role in fracture healing although their primary function is related to blood clotting (27). "Platelets are non-nucleated cells of the myeloid lineage" (28-30). The injured or damaged vessel produces and releases thrombin, a serine protease, which stimulates platelets to initiate the clotting process (28-30). The activated platelets orchestrate the response by forming the "fibrin thrombus", which acts as a "scaffold" for cellular engraftment. At the same time, platelets respond to the stimulus by secreting inflammatory cytokines (IL-1, IL-6, TNF-α) and growth factors (PDGF, TGF-beta), which triggers a cascade of events, involving the activation of other immune cells (neutrophils and monocytes), as well as mesenchymal progenitor cells (28-30).

Macrophages

Macrophages are myeloid lineage cells that are differentiated from monocytes. Macrophages, consist of various other cell subsets with different functions and are responsible for arranging inflammation and tissue regeneration after tissue damage (31, 32). Macrophages are some of the first cellular responders, which appear at the local hematoma and retain their presence throughout the healing process (14, 33, 34). Macrophages have been found to play a major role in bone homeostasis and bone fracture repair, since they act as "helper" cells to the osteoblastic and osteoclastic cell lineages, by taking part in the "crosstalk" and communication to maintain the balance in bone remodeling (1, 35). There are two main macrophage categories, based on their polarization (36); the M1 macrophages, which are termed also as "classically activated macrophages" (37) and the M2 macrophages, which are known also as "alternatively activated macrophages" (38).

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In a previous study by Schlundt *et al*. (2018), it has been suggested that the M1 macrophages are the first to infiltrate the bone fracture location during the "acute phase", while the M2 macrophages have been found to multiply in numbers during the "subacute" phase (39). Yet, the combination of both the M1 and the M2 macrophages is the machinery that play the significant role during the healing process, as they regulate both the early and late phases. This is indicated by the fact that time-dependent reduction of macrophages in either the "acute" or "subacute" phase leads to significant delay of bone healing (40). Additionally, it has been shown that macrophage inhibition, leads to a decrease in mesenchymal progenitor cell population, and thus inhibiting the ability of these cells to differentiate to osteoblasts (35, 41).

The exact machinery and molecular mechanisms, behind the action of macrophages in bone fracture healing is still unclear. It is certain that macrophages play a significant part in bone healing, yet it is still unknown how macrophages interact with the injured bone in order to procure repair. This is still a topic of intensive investigation and research (1, 3).

Neutrophils

The role of neutrophils in fracture healing remains unclear and involves many aspects of tissue repair. Neutrophils, are the most abundant granulocytes, as well as they are part of the polymorphonuclear family of immune cells together with basophils and eosinophils (42). They are activated by the presence of IL-1, TNF-α, which are produced by platelets (43). Neutrophils contribute both to the early stages of the inflammatory phase, as well as the later. In the early stages of the inflammatory phase they deposit the "fibronectin matrix", while during the later phases of inflammation, neutrophils remove the cellular and tissue debris, as well as they are implicated at the *thrombus* removal (44). Neutrophils are the first to arrive, on the fractured bone site, as they manifest anti-septic effects and also remove the damaged cells and other debris (23, 45, 46). The most significant role of neutrophils appears yet to be the release of cytokines (IL-1, IL-6, IL- 10, TNF-α, MCP-1, CXCL-1α, MIP-1) attracting monocytes, which will subsequently differentiate to macrophages (1).

T-Lymphocytes

T-lymphocytes, also known as T cells, are hematopoietic cells of the lymphoid lineage characterized by the expression of T- cell receptors (TCRs) (1, 3). A recent study on animal models has shown that T- and B-lymphocytes, appear at the fracture site three days after injury and subsequently their population reduces, when the physiological process of cartilaginous formation begins (47). It has been noticed that depletion of T-cells leads to reduced skeletal health and subsequently to a decrease in fracture healing (47, 48). Studies with mice have shown that subjects with lack of T- and B-lymphocytes have more "stiff" bones, more susceptible to fracture (49).

As aforementioned, T-lymphocytes regulate bone fracture healing and it is also known that white blood cells are present during both the primary and final stages of the bone repair process (50). T-lymphocytes consist of different sub-classes, which include the $T_{\alpha\beta}$-cells or $T_{\gamma\delta}$-cells, and their differentiation is defined by the expression of T-Cell Receptors (TCRs). The population of the $T_{\alpha\beta}$-cells is tightly regulated by positive and negative feedback mechanisms in the thymus. The regulatory mechanisms have as a result the maturation of $T_{\alpha\beta}$-cells, which subsequently express αβ-TCRs and co-receptors (51). Similarly, these cells will produce CD4+ T-helper (Th) cells, CD8+ cytotoxic T-lymphocytes (CTLs), and CD4+ regulatory T-cells (Tregs) (52). On the other hand, the $T_{\gamma\delta}$-cells are derived from the common cell of origin, as in the case of $T_{\alpha\beta}$-cells, but they recognize not antigen–specific molecules (53). These cells function as "sentinels" for the detection of microbe antigens and "self-components" released due to tissue stress, contributing to the intrinsic immune response. This function is facilitated by the production of cytokines and/or cytotoxicity (54). Further on, $T_{\gamma\delta}$-cells are subdivided into cellular subsets based on the expression of TCR-Vγ chains. Each cellular subset possesses its own characteristic tissue distribution and cytokine production pattern (55).

While $T_{\alpha\beta}$-cells exhibit "pro-inflammatory and anti-inflammatory functions" that are crucial for

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antigen-specific immune responses, $T_{\gamma\delta}$-cells are reported to be able to spread selectively to the tissue epithelium, where they exert defense and tissue repair functions, in the periphery (3). Recent studies have indicated that $T_{\gamma\delta}$-cells' population increases vastly during bone fracture, thus contributing to its healing by the production of IL-17A, which enhances bone formation (56).

A contrasting mechanism to the healing properties of T-cells, is derived from the presence of effector memory CD8+ T-cells. Effector memory CD8+ T-cells are found in abundance in the peripheral blood of patients with delayed fracture healing, while another experimental model has shown that when injected in mice, bone repair manifests significant delay to bone healing. These findings supported that fact that effector memory CD8+ T-cells suppress bone repair (57). This is also supported by the fact that effector memory CD8+ T-cells can produce TNF-α and interferon-gamma (IFN-γ), which participate to the suppression of bone marrow mineralization mesenchymal stem cells (MSCs) (3).

B-Lymphocytes

B-lymphocytes, also known as B-cells, are "hematopoietic cells of the lymphoid lineage", just like T-lymphocytes, and play a vital role in humoral immunity (1, 3). Depletion of B-cells is thought to be responsible for lessened bone health and decreased fracture restoration, same as the lack of T cells (47, 48). As in the case of all immune cells, B-cells are known to produce cytokines, which participate, with their turn, in the inflammatory processes (58). The B-lymphocytes that encounter their respective antigens, respond by an increase in proliferation and subsequently differentiate to plasma cells, which are further capable to produce body-defending antibodies. Some B-lymphocytes differentiate into "memory B-cells" that are prepared to act in re-infection. B-cell biology is very complicated, since they consist of several cellular subsets with different functions (3).

In the case of bone fracture healing, B-lymphocytes and T-lymphocytes have been found to play a role at the end of the inflammatory phase, and are again activated during the mineralization phase (50). The two cell populations act in contradictory roles. This takes place at the later stages of the inflammatory phase. On one hand, T-cells produce RANKL, which recruits, differentiates and activates osteoclasts and on the other hand, B-cells suppress the pro-inflammatory signaling through the suppression of IFN-γ, TNF-α, and IL-2 (59). At the same time, B cells also produce OPG, regulating in that way osteoclastic differentiation and activity (60).

In a recent report by Raggatt *et al*. (2013), supported the theory that B-lymphocytes do not play an important role in bone fracture healing. This came from the finding that mice with B-cell deficiency and in particular, with a μ-chain deletion, manifested no hindrance in bone fracture healing (61). However, later studies have highlighted that during bone injury (fracture) B-lymphocytes increase at the injury site, as well as in the peripheral blood, where they release IL-10. Consequently, B-cell related IL-10 reduced production, has been found to be s associated with delayed fracture healing (4, 48, 50, 58, 62). Despite current knowledge advancements, the role of different B-cell subsets in bone regeneration, is still largely unknown and thus further research is required.

Natural Killer Cells

Natural killer cells (NK cells) are "hematopoietic cells of the lymphoid lineage" and their function in fracture healing is not fully known (1). NK-cells are responsible for the recognition of aberrant or "strange" cells, as well as virally infected cells and their subsequent extermination. NK-cells are able to induced target-cell apoptosis, as well as, cell lysis through cytotoxic granules (63). This function in fracture healing is possible to be expressed by removing damaged cells in the injury site, while it has been shown that conditions at the fracture site inhibit NK cell-based cell lysis (64). However, it appears that the vital role of NK-cells is the "clean-up" or "debridement" of the injured tissue. This is believed to take place through the ability of NK-cells to recruit other inflammatory cells, osteoclasts, as well as the release of IFN-γ and RANKL (65). Noteworthy, Furthermore, they are known to play a vital role in tissue regeneration, through the recruitment

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of mesenchymal progenitor cells during the later stages of fracture healing (66).

Pro-Inflammatory Cytokines

In case of bone injury, an early event taking place is the interruption of blood supply and platelet aggregation with the release of platelet-derived pro-inflammatory cytokines. Such cytokines include the presence of IL-6, IL-1 and TNF-a (5). In addition, the early stages of fracture, include the formation of a hematoma, which aggregates inflammatory cells that further produce pro-inflammatory inflammatory cytokines and growth factors. The formation of this hematoma is crucial and its removal causes a defective bone healing (5, 67, 68).

Interleukin IL-6

A major player of inflammation is IL-6. It is released by numerous cells, as well as receptors for IL-6 are found on an additional abundance of cells. Numerous reports have highlighted the role of IL-6, which is found to exert multiple effects, as well as it is believed to stimulate osteoblastogenesis (69-71). IL-6 functions in a temporal pattern, as it is released within the first 24 hours after the injury (the bone fracture) promoting osteoblastogenesis through the differentiation of mesenchymal cells (including cells in the bone repair site). Thus, it is believed that IL-6 depletion is linked to healing impairment, which yet is compensated by the release of complementary factors that counterbalance IL-6 deficiency (3, 72-74).

Tumor Necrosis Factor (TNF)-a

The multi-purpose cytokine TNF-α, is mainly released by activated macrophages and is able to bind to TNFR1 and TNFR2 in order to activate downstream signal transduction (3, 75). The role of TNF-α is crucial to bone physiology, since animal models have shown that aberrant expression of the cytokine is linked to chronic inflammatory poly-arthritis (76, 77). The exact mechanism of arthritis induction by TNF-α is still unknown, yet it is believed that induces a Wnt signaling inhibitor, in synovial fibroblasts, and thus suppresses bone formation in the arthritic joint. On the other hand, it is shown that TNF-α promotes bone restructuring in cases of fracture (78, 79). Interestingly, *in vitro* experiments, in which mesenchymal cells treated with TNF-α, manifested contradictory results, as in some cases TNF-α promoted and in other inhibited bone formation. These distinct functions bring up the role of bone fracture microenvironment, as it appears that it regulates TNF-α functions (3).

Interleukin IL-17A

Initially, IL-17A was known to be produced by Th17 cells and later it has been found that they are also produced by the CD8+ T-cells, $T_{\gamma\delta}$-cells, invariant NK T-cells, NK cells, Lymphoid Tissue inducer (LTi) cells, B-cells, and mesenchymal cells (80-84). The role of IL-17A, in bone physiology, has been found that is linked to inflammatory bone loss in erosive arthritis, as well as it has been found that it sustains the body physiology against bacteria and fungi by stimulating the release of antimicrobial peptides and neutrophils recruitment (3). Furthermore, several studies have reported that IL-17A promotes bone regeneration, as well as it has been used for therapeutic purposes, since anti-IL-17A antibody is effective against arthritis (85, 86).

In the case of bone fractures, IL-17A has been found to also play an important part. In particular, it has been reported that IL-17A is activated during the "early phase" of bone fracture healing and it is mostly released by $T_{\gamma\delta}$-cells (25, 56). In addition, it is reported that IL-17A promotes the mesenchymal cells proliferation on the injury site, and stimulates their differentiation to osteoblasts (56). As aforementioned, since IL-17A is released at the timepoint immediately after the injury, it is believed that it is a cytokine that regulates the early, primary osteoblastogenesis (3).

Osteoclasts

Osteoclasts are "multinucleated cells of the myeloid lineage" and they can differentiate directly from monocytes, as well as from macrophages (87). Although, osteoclasts were initially believed to be strictly bone-related cells and thus not immune-related cells, recent findings have shown that they play a major role in the immune response. In par-

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ticular, they are thought to act as indirect mediators of immunity, since they are able to release factors that can activate the innate immunity, but also inflammatory signals lead to their differentiation and activation (1, 35, 88). Their main role in bone physiology is that of "bone phagocyte". This name is derived from their specialized property and ability to resorb bone matrix (89).

The primary mechanism of osteoclast function, comes from the differentiation of monocytes, which are assembled to the fracture-site, differentiating to osteoclasts. Osteoclasts are primarily activated by RANKL (1, 35), whose primary source are the osteoblasts. Besides osteoblasts as sources of RANKL, NK-cells and activated T-cells are also able to produce RANKL during fractures. Further on, another molecule that participates in osteoclast activation is osteoprotegerin (OPG). OPG is a "decoy" receptor, which binds to RANK and inhibits RANKL binding, thus preventing osteoclast activation. OPG is released by osteoblasts and B-cells during fracture healing (1, 35).

Conclusions

It has become evident that the immune system plays a critical role in the process of bone fracture healing and restructuring. The process of bone fracture healing includes three main phases. These are epigrammatically; Inflammation, repair and remodeling. During the stage of inflammation, which is considered crucial, the mechanisms of innate and adaptive immunity, along with the respective cells assist to the process of bone debris removal, anti-sepsis and preparation of the microenvironment for the upcoming event of mesenchymal differentiation. The stage of inflammation involves the interaction of macrophage/osteoclast lineages, both contributing to the phase of inflammation. During the next phase, the repair phase, the multi-potential stromal cells, are taking charge in order to start bone repair. Multi-potential stromal cells, are cells possessing a trait of adherence capacity, which express surface molecules such as CD90, CD73, CD105, but not hematopoietic lineage markers. Multi-potential stromal cells, are the ones that are able to differentiate into bone, fat and cartilage cells, where in the case of bone healing they differentiate to chondrocytes (5, 90).

Although, initially it was thought that immune cells participate during the phase of inflammation in the bone healing process, later studies have shown that they are also active during the repair phase. Immune cells, during the repair phase, function as mediators of mesenchymal differentiation, as well as they play an important role to convert "soft *callus*" into "hard *callus*". Another responsibility of immune cells is the assistance to the formation of vasculogenesis in the injured bone. Finally, it has been shown that the mesenchymal stromal cells, active during the repair phase, mediate the function and interactions of osteocytes and in particular, the interaction between osteoclasts and osteoblasts. Cells revealed to play such a role, have been reported to be the macrophages and probably the Th17 lymphocytes (5).

In conclusion, immunity is the first biological machinery implicated during injury and in particular, during bone injury and damage. Immuno-cells, play a significant role as they, restore vasculature, initiate signaling cascades and recruit cells to complete the repair processes. Thus, immune system can be considered to be a potential therapeutic target for bone fracture healing. However, the exact mechanisms on the interactions between bone physiology, homeostasis and the immune still are still largely unknown. Intense research is already at play, which is required in order to better appreciate the biological significance of immune cells in bone regeneration.

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REVIEW

Transient osteoporosis of the hip

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ABSTRACT

Transient Osteoporosis of the Hip (TOH) is a rare syndrome that Orthopaedic surgeons deal with. This review emphasizes the importance of clinical suspicion that a physician should possess when examining a patient with hip pain and no prior history of trauma. Specific findings like Bone Marrow Edema (BME) play an essential role in discriminating TOH from similar clinical entities with a worse prognosis. Once a definite TOH diagnosis is established, the patient can be treated conservatively with a satisfactory functional outcome.

KEY WORDS: Hip, Pain, Bone Marrow Edema

Introduction

Transient Osteoporosis of the Hip is a rare condition, however more common in middle-aged men [1]. To a lesser extent, it may affect other weight-bearing joints, such as the knee, the ankle, and the foot [1]. Bone Scintigraphy reveals a promoted activity in both the femur and the acetabulum, though not in the surrounding soft tissue. Initially described in third-trimester pregnant women, albeit affects almost all ages and sex groups. The pain typically subsides after six to twelve months, and the radiologic image is gradually restored. The exact etiology is by and large unknown, yet there has been considered proof that local bone marrow edema plays a significant role. Some investigators suggest that TOH is a form of early-stage reversible avascular necrosis of the femoral head [2]. The overwhelming majority of cases do not require a specific treatment regimen, per se. Apart from using over the counter analgesics, extreme pain may be alleviated through femoral drilling.

Pathogenesis

While TOH's etiology remains by and large unclear, several theories have been proposed, the vast majority of which has to do with bone remodeling and vascular phenomena. Curtiss and Kincaid first attempted an explanation with their neurogenic compression theory. They reckoned that the child's head puts pressure over the mother's obturator nerve, as a possible TOH mechanism during the third trimester of pregnancy. According to recent studies [3,1,4], there are three stages in the disease's evolution: the initial fracture or neurovascular attack, the bone resorption, and the resolution. Lately, three new mutations in genes LRP5, COL1A1, and COL1A2 have been related to early-onset osteoporosis of the hip in pregnant women [5]. Another theory, based on the hormonal changes during pregnancy, connects PTHrP with TOH. Nowadays, TOH's common knowledge affects both sexes with a male to female ratio of 3:1 [6, 7]. Patel described cases of BME detected on MRI in patients with the rheumatological disease [8]

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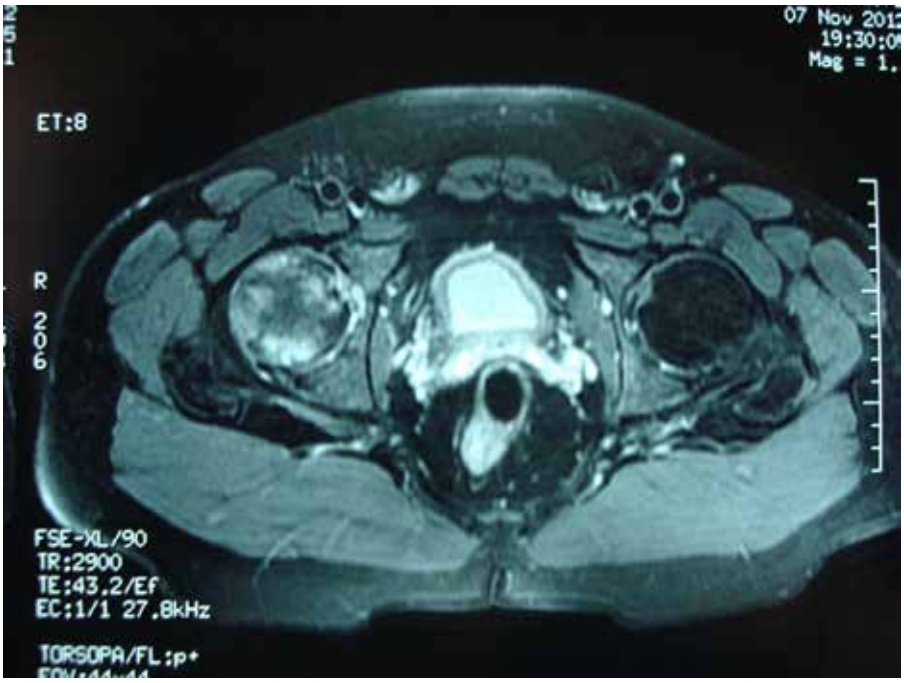

Figure 1. *Transverse T2 image of both femoral heads with a highly heterogeneous signal on the right side*

Rosen proposed that an obstructed venous drainage could lead to local hyperemia and the femoral head's demineralization, a common finding in these patients [9]. Hofmann et al. in 1993 assumed that Transient Osteoporosis is nothing more than a reversible ischemic attack, followed by rebound hyperemia in the surrounding bone [10]. Histologic examination of bone and bone marrow specimens showed no signs of necrosis [11].

Proximal Nerve Roots theory suggests that a microvascular injury affecting the small vessels near the proximal nerve roots would lead to transient denervation, also contributing to TOH symptoms [12]. The time course in which the TOH subsides symptoms indicates the time that this kind of nerve injury requires to heal. In a similar direction, some find a resemblance to Reflex Sympathetic Dystrophy and Complex Regional Pain Syndrome. Undoubtedly, bone marrow edema is the main event that is related to TOH. A possible mechanism would be a local hypervascularity, leading to increased capillary permeability. This theory gains ground since it is also supported by angiographic and scintigraphic studies [13].

Finally, Regional Accelerated Phenomenon activation due to noxious stimuli would cause a turnover process ten times that of a normal bone. Transient osteoporosis of the hip has also been described in patients following bariatric surgery [14].

Symptoms and diagnosis

Typically include a sudden onset of increasing unilateral hip pain, usually alleviated when the patient lies down. There might be a moderate decrease in hip motion range, mainly in abduction and rotation [15], and the patient may walk with a noticeable limp [16]. In rare cases, there might be bilateral involvement of the hip joints [17].

Some particular imaging studies are used to set the diagnosis of TOH. After receiving a full medical history, that is emphasized on the duration and the various characteristics of the pain related to the condition as mentioned above and examining the patient clinically. Inflammation indicators such as ESR may be elevated, though they are in no way a specific study that we can rely on when establishing a diagnosis.

The hip's conventional radiography would be the initial evaluation in most diagnostic endeavors, as shown on AP and lateral views. The common find-

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ings are subchondral bone loss, joint effusion with a preserved articular space, while osteopenia is rarely evident in the first 1-2 months, as well as any possible microfractures [18]. In later stages of untreated TOH, few patients' X-rays present the so-called "phantom appearance" of the femoral head, namely a complete absence of its bony features [12]

An alternative evaluation of classic X-ray investigation seems to be bone scintigraphy. It detects lesions in the bone during the first stage of TOH – the main disadvantage of conventional radiography. Furthermore, the increased radionuclide uptake in the femoral head is quite useful in distinguishing TOH from avascular necrosis in the early stages. Although used and described in the literature, computer tomography and ultrasound of the hip are not sensitive enough.

MRI is the gold standard when dealing with TOH (fig. 1). It is a study both sensitive and specific enough to set the diagnosis along with the clinical findings and medical history. And that is mainly since MRI is the sole adequate test to assess bone marrow edema. Classical results include a low-intensity signal in the T1 sequence, with a loss of the local tissue's expected fatty appearance and a high-intensity signal on T2.

Differential diagnosis

TOH is characterized by acute disabling pain without a prior history of trauma. There is a focal loss of bone in the histologic examination. First radiologic findings are evident 3-6 weeks after the initial symptoms. Bone loss could be extensive, but the vast majority of cases present spontaneous improvement. As far as imaging is concerned, osteopenia is found on later stages' X-rays and bone scintigraphy reveals increased radionuclide uptake. Bone marrow edema on MRI is evident 48 hours after the onset of pain [19].

Migration occurs in 5-40% of patients with TOH. Unlike TOH, inflammatory changes of the skin may be present. Usually, migration happens towards a neighboring joint. Sometimes TOH is described under the common term "Transient Regional Osteoporosis." A paramount aspect of diagnosing TOH is distinguishing it from avascular necrosis of the femoral head [19]. The latter usually affects the bone's superior anterior surface and is typically found in the hip or knee. There are no early signs of bone marrow edema on the MRI scan. "Double line" sign on T2 is considered to be pathognomonic. On the T1 sequence, low signal intensity lesion is pathognomonic. The femoral head's vascular necrosis is commonly associated with alcohol abuse and corticosteroid treatment and presents a high incidence in Japan [20]. An MRI scan with intravenous contrast administration would help differentiate TOH from neoplastic conditions such as multiple myeloma, lymphoma, leukemia, and metastatic bone disease. Inflammatory arthritis would present with elevated lab tests such as ESR, CRP, and WBC. It would also include periarticular imaging signs like soft tissue involvement and joint effusion, apart from the hip's transient osteoporosis.

Treatment

The overwhelming majority of TOH cases are treated non-operatively. In some patients with intense hip pain, drilling of the femoral head may help, though there seems to be no clinical advantage over pharmacotherapy [1]. The typical instructions include avoiding weight-bearing and paracetamol.

Intravenous bisphosphonate therapy has been proposed to restore average bone density in the region, together with nutritional measures, namely calcium and vitamin D [13, 21]. Iloprost, a prostacyclin analog, dilates vessels and reduces bone marrow edema [20]. Trevisan and Ortolani suggest periodic evaluation of densitometry throughout TOH treatment to adjust weight-bearing instructions [22].

hysical therapy and aqua exercise help patients so that hip movement is secured without further loading of the affected joint. In other cases, there is always the risk of a stress fracture. The pulsed electromagnetic field seems to be a promising new treatment [23] and hyperbaric oxygen therapy [24], although there is not enough literature to support them. A time course of approximately 6-8 months is required until adequate resolution of the symptoms. Treating the patient with a salmon calcitonin injection daily has been shown to reduce the pain and shorten the disease [25].

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TABLE 1.

Differential diagnosis		
1	Osteonecrosis	Past medical history, Radiologic signs
2	Inflammation	Elevated WBC, ESR, CRP
3	Neoplasia	Exclusion by MRI findings

TABLE 2.

Treatment options		
1	Drilling of the femoral head	May cause some pain relief
2	Calcitonin, Bisphosphonates, Teriparatide	Shortens course of the disease
3	Pulsed electromagnetic field, hyperbaric oxygen	No adequate data

Discussion

Diagnosing TOH is quite tricky in most cases as the usual presenting symptom is the acute onset of pain. The treating physician should keep in mind that TOH can migrate to other joints, primarily those bearing weight (e.g., the knee). The widely accepted pathophysiologic hypothesis is that a primary insult causing vascular disturbance and microfractures may result in bone marrow edema diminishing the bone trabeculae, resulting in temporary bone loss [26]. The additional vulnerability determined by pregnancy is also inadequately described. However, the loss of calcium imposed by the required transfer to the fetus, particularly towards the end of pregnancy, may play a role. Overload set by the weight increase during the third trimester also contributes to the pathology, as mentioned above. It may play a role in the higher incidence of fracture observed during this period [1]. Finally, an osteoporotic or osteopenic background probably acts as an additional variable, as indicated by the anti-resorptive treatment's satisfactory clinical outcomes [27].

MRI is the gold standard diagnostic tool suggested by the past literature [1]. Its role is critical in differentiating TOH from AVN and ruling out traumatic injury, fracture, degenerative processes, inflammatory diseases, ischemic injury, infection, and neoplasia [3]. Early detection and correct diagnosis can prevent unnecessary surgical intervention, usually employed in cases such as BME. Based on reported cases in the literature, medical therapies (including teriparatide, zoledronic acid, or a combination of alendronate and calcitonin) could reduce the duration of symptoms [1]. Core decompression shows no better results than medical therapy [1]. Adjustment to a lifestyle with limited weight-bearing and physical therapy also seems to be beneficial for the patient.

In recent years further clinical details have been unveiled regarding TOH, though the exact pathologic mechanism remains unclear. If left untreated, it may progress into avascular necrosis or even fracture [1]. Every treating physician's primary target should be alleviating the symptoms while establishing an early diagnosis and excluding similar clinical entities.

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ORIGINAL

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The Cost of Road Accidents in Athens

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ABSTRACT

Road traffic accidents are a contemporary matter of our society as they can have dire physical, mental and socioeconomic consequences. The purpose of this report is to highlight the cost of road accidents that occur in Greece, treated in General hospital of Athens "G. Gennimatas" from 22/01/2018 until 20/03/2018. During this period of time our Emergency Department treated 135 victims of road accidents, 81 males 54 females. Due to the fact that our institution treats only adult patients, no patients under the age of 15 were included in the study. 57% of the victims, 77 patients needed hospitalization, 3 people were dead at the time of arrival and 55 patients were discharged home after the examination. There were 82 motor accidents, 4 cyclist drifting, 9 pedestrian drifting and 40 car accidents. The minimum immediate cost of a road accident victim is calculated at 38.99 euros, in cases where the patient had no severe injury and was discharged home. On the contrary, the cost of a polytrauma patient requiring hospitalization starts at 400 euros and can rise in extreme cases into the hundreds of thousands of euros. The immediate cost of a road traffic accident cannot be compared to the total physical, emotional and economic cost, which is associated with a prolonged recovery, disability or even loss of life. Consequently, preventive measures and constant vigilance in improving trauma care are essential in minimizing the socioeconomic impact of road traffic accidents in Greek society.

KEY WORDS: road accidents, cost, polytrauma patient, road safety

Introduction

Road traffic accidents are a major international health hazard with nearly 1.3 million people dying on road crashes each year, that is, on average, 3,287 deaths a day [1]. In addition 20-50 million people are injured and disabled every year resulting in an increase of costs of hospitalization, rehabilitation and living. The affected groups are children, pedestrians, cyclists and senior citizens and over 90% of all road fatalities occur in low and middle-income countries, which have less than half of the world's vehicles [2]. Consequently, modification of driving behavior, proper equipment and suitable road surface can lead to a substantial decrease in both the death toll and injury burden related to RTAs [3] [4] [5] [6].

Our study is a cross sectional observational study from 22/01/2018 until 20/03/2018. The data include all victims of road accidents such as car accidents, motor accidents and pedestrian drifting. We calculated all costs from the time that the patient presents at our Emergency department until home

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discharge or death.

Material and Methods

During this period of time our Emergency Department received 135 victims of road accidents, 90 ambulatory and 45 non- ambulatory, 81 males and 54 females. Due to the fact that it is an adult trauma hospital no patients younger than 16 years old were included. Most of the victims, 77 patients needed hospitalization, 3 people were dead at the time of arriving and 55 patients were discharged after the examination. There were 82 motor accidents registered, 4 cyclist drafting, 9 pedestrian drafting and 40 car accidents.

The primary survey aims to identify and immediately treat life-threatening injuries and is based on the ATLS resuscitation protocol. Ambulatory patients without obvious injuries, GSC 15/15 normal SpO_2 and normal Blood Pressure underwent the first hemoglobin measurement on arrival, a chest x-ray, a FAST ultrasound examination, a two- hour observation at the emergency department and a repetitive hemoglobin measurement before they were discharged. Patients with thoracic, spinal or limb pain, open injuries or alteration of sensation underwent additional clinical exams, and imaging of the injured area.

The Patients were continuously being evaluated from the time they were presented in the emergency room, according to the international triage system; green for walking patients, yellow for urgent patients who were unable to walk, red for patients who needed immediate care and black for dead people. Patients transferred by ambulance and the patients unable to walk, after the ATLS protocol were categorized in yellow or red color according to international triage system. The yellow and red category patients underwent vein catheter insertion, Haemoglobulin measurement, biochemical measurements (Glucose, Creatinine, Urea, Sodium, Potassium, Serum Glutamic Oxaloacetic Transaminase, Serum Glutamic Pyruvic Transaminase, Lactic Acid) blood cross test, chest x ray, U/S FAST and x-rays of the injured areas. Computed tomography scans were necessary in cases as craniocerebral injuries, chest and sternum trauma, multiple broken ribs, respiratory insufficiency, abdomen pain with suspicion of hemorrhage. Furthermore, skeletal injuries including spine trauma and joint fractures required CT scan. In Greece each X-ray costs 4,05 euros, U/S FAST costs 29,18 euros for male and 35,49 euros for female patients, the CT of each area costs 71,11 euros.

As far as the blood analyses were concerned, blood testing with full blood count costs 2,88 euros while biochemical tests 22,86 euros, and the blood cross matching test costs 5,22 euros. We must also take under consideration expenses attributed to consumables, like intravenous serums, antibiotics, painkillers, urine and rinogastric catheters that was found to have a great variance in our study group.

Results

According to our findings, the minimum cost per road accident victim was 38,99 euros, for a patient that had no severe injuries and was deemed safe to go home. In contrast the cost of a polytrauma patient who needs hospitalization starts at 400 euros including chest and pelvis x-rays, CT scan, blood tests, painkillers, Normal or Ringer's solution serums etc. In our study the distribution of injuries was: soft tissues injuries amounted to 88 (65.2%), 45 (33%) persons had head injuries, 26 (19%) had facial bones injuries, 63 (46%) persons had thoracic cage injuries, abdominal injuries were diagnosed in 13 patients (9%), long bone fractures amounted to 70 cases (51%) and 19 (14%) had spinal injuries.

Consequently, the majority of victims of road accidents suffer from either a minor or severe skeletal injury. Analyzing the skeletal injuries of the road accidents people had bony injuries, upper limb 22 (24%), lower limbs 27 (30%), pelvic ring factures14 (0.15%), 17 (19%) had spinal fracture while 9 (10%) had multiple fractures. According to our data 39 patients were treated operatively, 30 required conservative therapy and hospitalization, and 20 were discharged home without hospitalization. Specifically, the majority of long bones injuries required operative treatment, all pelvic ring fractures needed at least one day hospitalization and ten spinal fractures hospitalized. Due to the great number of skeletal injuries, most of patients of road accidents are

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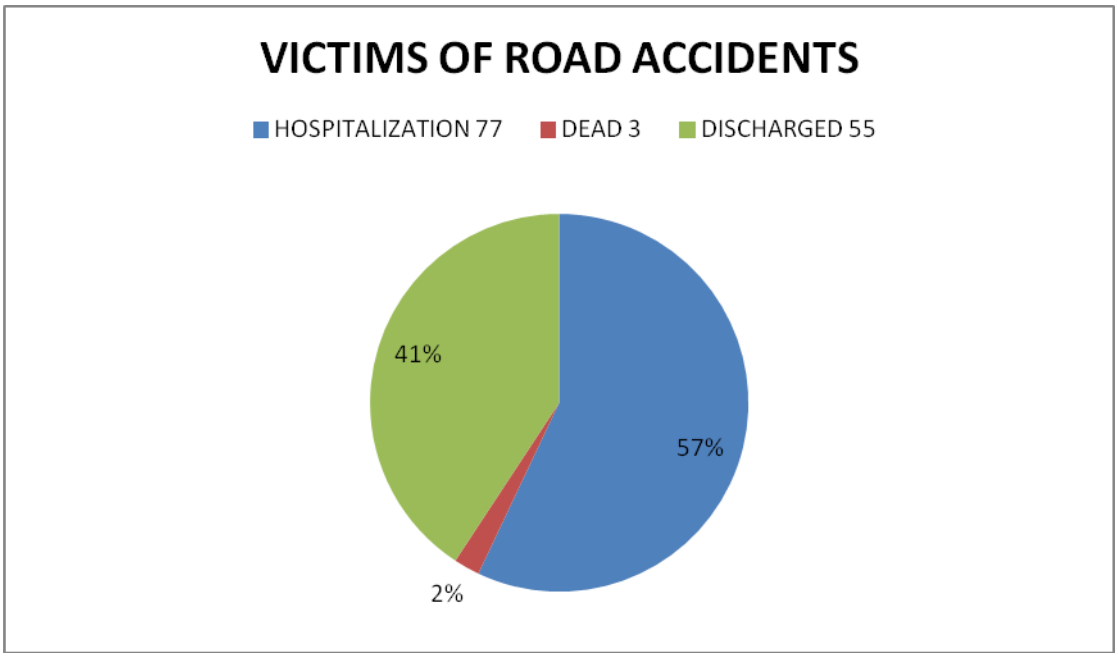
TABLE 1.

Victims of Road accidents and Hospitalization



hospitalized in orthopedic department. It is therefore extremely significant to analyze the cost of day care in the clinic as well as the cost of each orthopedic procedure.

Injuries such as ligament sprains, non-displaced fractures and fractures not necessitating surgical treatment, are usually treated with a splint or a cast that costs on average 2 euros in case it is made of plaster or 6 euros if it is made of synthetic material. Radiographic imaging including a minimum of two views before and after the cast placement is also required, with a total cost calculated on average to be in the range of 14-18 euros. In our department during the study period 17 intramedullary nailing procedures were recorded due to proximal femoral, femoral shaft or tibial shaft fractures. The average implant cost is 700 euros, so in total 11,900 euros were spent for these treatments. Moreover 5 bipolar hemiarthroplasties were performed with a cost of 500 euros each, and a total of 2500 euros. Finally, 5 lower limb fractures were treated with osteosynthesis utilizing special plates with a total cost of 1500 euros. Concerning the upper limb injuries, most cases were humeral shaft fractures and were treated non-operatively, with a cast or a sling costing on average 3to 5 euros. Two proximal humeral fractures, however required a hemiarthroplasty costing around 600 euros each and ten fractures were fix with osteosynthesis using plates with total cost of 6500 euros. Summarizing, in our orthopedic department during these months 39 patients required operative treatments with an average 3-day hospitalization and 30 patients who underwent conservative treatment but needed on average a two-day hospitalization.

We must also take under serious consideration the cost of the anesthesia, blood transfusion in some cases, antibiotics and painkillers. It would be of great interest at this point to indicate a report of Cost Benefit Analysis of Strategy for Road Safety in Ireland, in which the Hospital in- patient cost is being recorded. "Hospital in-patient costs refer to the costs of keeping a patient in hospital and providing them with treatment for their injuries. In the BTE report, these costs were assumed to be directly proportional to the length of time in hospital. Approximate-

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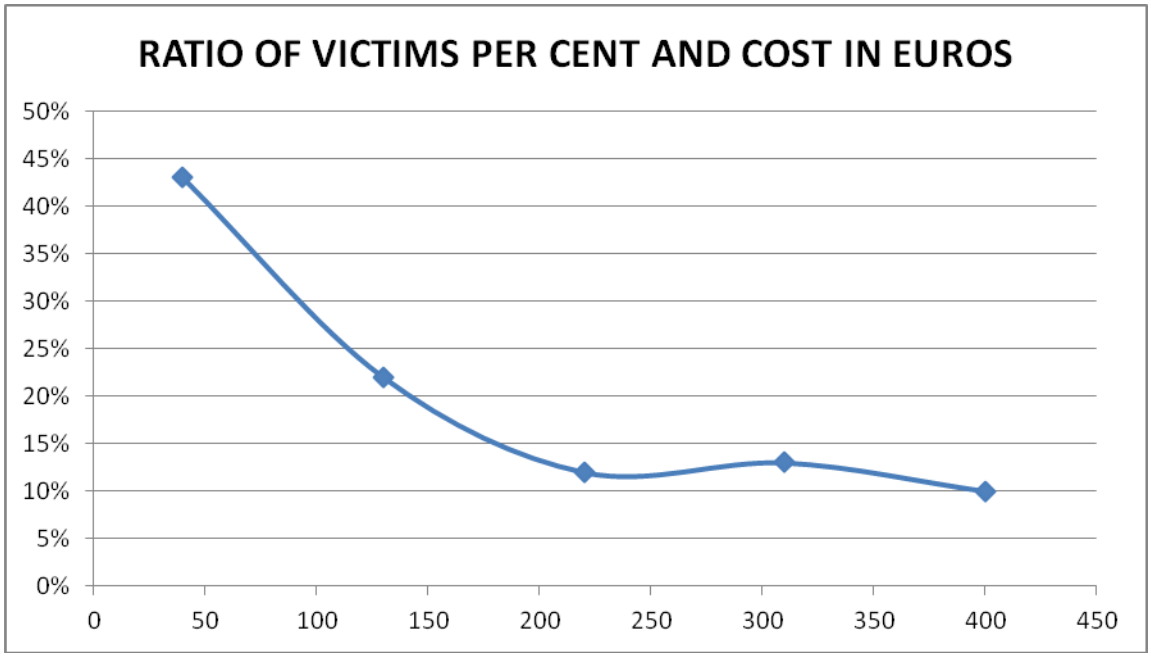
TABLE 2.

Range of Victims per cent and cost in euros



ly a third of fatally injured crash participants (681 out of 1,970) died after admission to hospital. These fatally injured crash participants were estimated to have been in hospital for six days. The average stay in hospital for patients with serious injuries was 8.3 days. A small proportion of crash participants with minor injuries was treated at hospital and their stay in hospital was estimated as one day. The estimated costs per crash participant given in the BTE report were $1,373 for a fatality, $5,493 for a serious injury, and $28 for a minor injury. It can be seen that the total cost is over ten million dollars."[2].

Discussion

Road traffic accidents carry a lot of additional costs for our welfare state system because they are the principal reason of disability. Minor injuries such as strains require at least 3-day recovery leave and follow up visits of the patient, while severe injuries need at least one to three months recovery leave, physiotherapy sessions and a plead of re-examination appointments. Therefore, RTAs result in substantial mortality and years of potential life lost, provoke permanent or impermanent damage to the patient and reduce directly or indirectly lead to loss of work hours especially among the younger more productive patients [7] [8] [9]. Consequently, RTAs have a negative effect not only on the victims' personal lives but also the economy of each country. Moreover, in many cases road accidents result in court proceedings. The study of CDC about morbidity and mortality, in US in 2012, shows that the nonfatal injury burden is also high. For each motor vehicle occupant killed in a crash in 2012, eight were hospitalized, and 100 were treated and released from the ED. "The estimated lifetime medical cost of nonfatal crash injuries is similar to other serious, but perhaps more well-known, public health problems. For example, the estimated lifetime medical cost of crash injuries is approximately 50% higher than the estimated $12.6 billion cost for human immunodeficiency virus (HIV) in the United States [4] [10]. On average, each crash-related ED visit costs $3,362, and each hospitalization costs $56,674. These nonfatal crash injury costs can create both an immediate and lifelong burden for individuals

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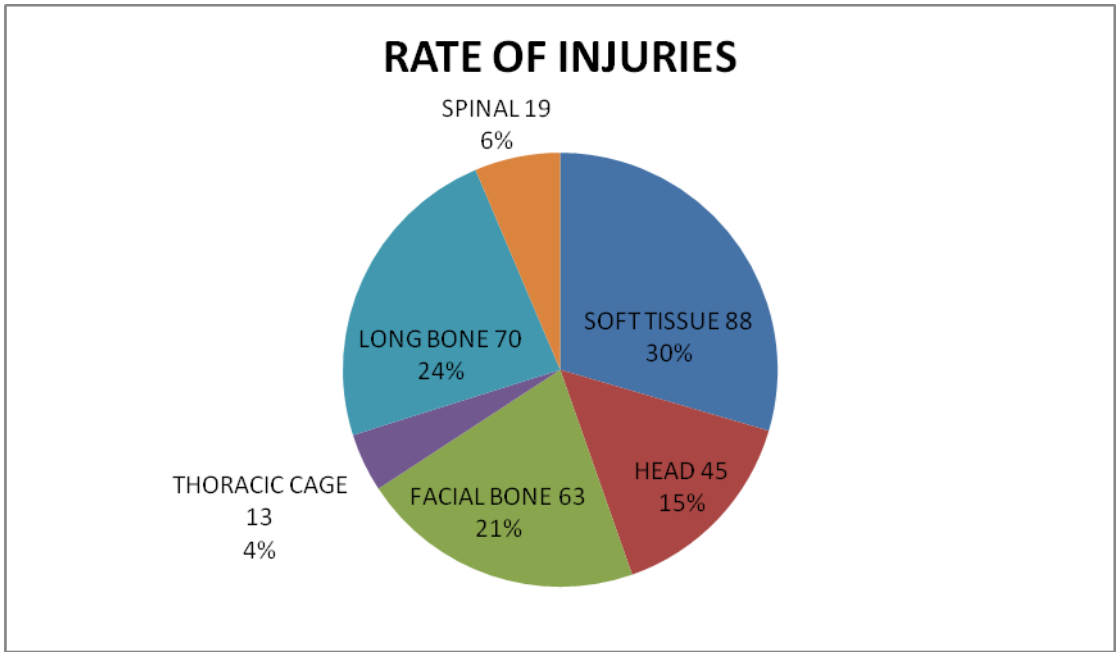
TABLE 3.

Rate of Injuries



and their families, as well as employers, and public and private health care payers. Although these are lifetime medical costs, the majority of medical costs (approximately 75%–90%) are estimated to occur in the first 18 months after the crash [7] [9]. In addition to the burden of medical costs, crash injuries cause a substantial lost lifetime productivity valued at $32.9 billion." [3] [5].

According to these results, it is evident that road accidents are part of a serious phenomenon. Distracted driving is a dangerous epidemic on Highways. According to the National Highway Traffic Safety Administration distraction plays a key role in over 3,000 road deaths and injuries each year. Distracted driving crashes are crashes in which drivers lose focus on the safe control of their vehicle due to manual, visual or cognitive distraction [1]. In contrast, Fatigue-related crashes are most common in very early morning hours and mid-afternoon. The risk increases when driving long distances or on monotonous roads. The chance of serious or fatal injuries increases due to slower driver response time [1]. Road traffic accidents as a global challenge are on the global agenda through Sustainable Development Goals SDG 3 and 11 which aim to half the number of global deaths and injuries from road traffic accidents by 2020. Moreover to provide access to safe, affordable, accessible and sustainable transport systems by improving road safety by 2030. Most of fatal cases according to their involvement in traffic, is among drivers. Regarding contributing factors, the driver is responsible on average of 99.3% for entire period 2010-2015 whereas climatic conditions only 0.5% and technical vehicle condition 0.1%. Similar results were found in different studies, in the United Arab Emirates, driving behavior are more prevailing contributing factors, and vehicle safety is least [3] [5]. In South Africa the drivers' behavior was the main cause of accidents (46%) [10] [11] [12]. In Taiwan, human factor is responsible up 3 to 4% for road accidents [13] [14].

Unfortunately, car accidents in Greece are caused by a combination of reasons. Number one reason is our driving behavior, followed by inadequate police supervision (which results to a loose attitude of drivers towards laws and regulations). Third

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reason is the aged "car fleet" in Greece, especially when compared to the European average and the badly maintained roads and vandalized traffic signs [13] [14].

In our country this is the present situation, Greek statistics for road accidents rose by 12.3 percent in April compared to the previous year, according to the Hellenic Statistical Authority of Greece (ELSTAT). The data included road accidents that caused death or injury. The number of accidents came to 1,065 compared to 948 in April 2015 [6] [13] [14].

The Hellenic Statistical Authority (ELSTAT) announced provisional data on Road Accidents for January 2018. In particular, the road traffic accidents which occurred in Greece, resulting in death or injury, increased by 18.8% in comparison with the corresponding month of 2017 (757 road accidents in January 2018, against 637 road accidents in January 2017). The casualties of the injury-causing accidents that occurred in January 2018 were as follows: 38 deaths, 49 serious injuries and 845 slight injuries. In contrast, in January 2017 the corresponding figures were: 54 deaths, 41 serious injuries and 747 slight injuries. Therefore, road accident casualties in January 2018 decreased by 29.6% for deaths, increased by 19.5% for serious injuries and increased by 13.1% for slight injuries [13] [14]. Data shows that most accidents occurred in Athens, whereas the north Aegean had the more serious accidents in terms of death and injuries, followed by the Ionian and the Peloponnese [13] [14]. The aforementioned numbers place Greece 28th in terms of number of accidents and last place in the European Union.

In conclusion, the implementation of policies that cover all aspects of road safety, ranging from car design and road network upgrades to enforcing safe driving behavior is vital in order to prevent and reduce the impact of road traffic accidents both in terms of human loss and disability and the substantial direct and indirect costs incurred at a national level.

The authors declared no conflicts of interest.

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CASE REPORT

Diffused Pigmented Vilonodular Synovitis / Diffuse Type Tenosynovial Giant Cell Tumour of the knee treated with arthroscopic synovectomy and adjuvant Yttrium local infiltration. A case report, a "safe treatment algorithm" and the peer literature

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ABSTRACT

Pigmented villonodular synovitis (PVNS) is a unique mesenchymal lesion that arises from the synovial tissue of the joints. It is divided into a localized type (LPVNS) and a diffuse type (LPVNS) also known as Tenosynovial Giant Cell Tumor. The latter, is a predominantly intra-articular, aggressive, infiltrative process, characterized by both inflammatory or neoplastic properties and local destructive progression. A high recurrence rate is observed after surgical synovectomy alone. The positivity of colony-stimulated factor 1 (CSF1), its receptor (CSF1R), and receptor activator of nuclear factor kappa-B ligand (RANKL) with the clinical outcomes and the recurrence rates is a field of interest in therapeutic targeting with the use of biological factors/agents such as anti-TNFa. Adjuvant intra-articular injection of Yttrium-90 in the immediate post-operative period effectively reduces the rates of local recurrence. We present the case of a 59-year-old female patient with diffuse PVNS of the left knee treated with arthroscopic synovectomy and adjuvant Yttrium-90 local infiltration following a "safe treatment algorithm".

KEY WORDS: Pigmented Villonodular Synovitis, Arthroscopic Synovectomy, Biological factors, Yttrium-90 infiltration

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A 59-year-old female patient presented to our clinic reporting gradual onset of debilitating left knee pain over the course of the last 12 months. Pain was accompanied by joint effusion and stiffness during the last 9 months. The patient had been already treated conservatively by means of non-steroid anti-inflammatory medication (NSAIDs) and paracetamol per os intake, platelet rich plasma (PRP) intra–articular injections and physiotherapy without any significant improvement. The patient denied any history of trauma. Her medical history included hypertension and thyroidectomy for which she was currently being treated with Perindopril, Ramipril\hydrochlorothiazide and Levothyroxine respectively.

On clinical examination, cardinal manifestations included a large left knee joint effusion accompanied by diminished range of motion ranging between 0 to 110 degrees. Plain radiography failed to identify any specific pathology. However, the Magnetic Resonance Imaging (MRI) set the diagnosis of Diffused Pigmented Villonodular Synovitis (PVNS) (**Fig. 1**) and the "safe treatment algorithm" was implemented. (**Table 1**) This treatment algorithm is applied in our department as a standard procedure according to evidence-based medicine.

The patient underwent arthroscopic synovectomy through two main (antero-lateral and antero-medial) and one accessory (postero-medial) portals. Hypertrophic synovitis of characteristic brownish appearance, along with hemorrhagic fusion were the main arthroscopic findings. (**Fig.2**). Synovial tissue biopsies were obtained for histopathologic examination and synovial fluid samples were sent for cytology. Meticulous removal of the inflammatory synovium was then performed. The hazardous removal of the synovial membrane off the posterior wall was accomplished through the postero-medial portal as well as through the intercondylar approach between the anterior and posterior cruciate ligaments. The patient remained hospitalized for 24 hours and discharged with instructions including cryotherapy, mild kinesiotherapy and load bearing as tolerated with the use of crutches.

Histological examination revealed the papillary configuration of the membrane, the local presence of multinucleated osteoclastic type giant cells and monocytoid cells and the deposition of haemosiderin confirming the preoperative diagnosis of PVNS. (**Fig.3**)

Six weeks post-surgery, a Tc-99m bone scan was performed to assess the presence of any residual synovial tissue. (**Fig.4**) A week later, under radiological guidance and aseptic conditions, arthrography of the affected knee was initially performed with the use of a 2 ml contrast agent (lobitridol 350mg/ml, XENETIX, Guerbet Inc., France) in order to confirm the integrity of the synovial capsule. (**Fig. 5**) Aspiration of almost 10ml joint fluid was performed in order to reduce the intra-articular volume and 1.5 ml of Yttrium (^{90}Y) 5 mCi was subsequently injected into the joint. Finally, a flush of 2 ml of hydrocortisone was administered to reduce any local reaction as the needle was withdrawn. The joint was then passively mobilized throughout its range of motion for one minute to facilitate the distribution of the radiological agent to the synovial capsule. A Robert-Jones bandage was applied to the knee. A Geiger counter close to the affected joint, ensured that no systemic environmental leakage of ^{90}Y took place. At the end of the procedure, almost one hour later, a bone scan was conducted to rule out any systematic leakage of ^{90}Y in the extra-articular space. (**Fig. 6**) The patient was discharged with instructions to rest and keep the involved extremity in full extension for two days.

At the first follow up, 2 days later, the patient had no side effects of leakage, joint swelling, febrile reactions or skin irritation. Range of movement was almost normal and the patient was allowed to return to her daily activities. At 6-month and 1-year follow up, the patient remained asymptomatic with a fully functional joint. The patient was discharged from clinic; however, she was advised to report back any symptoms related to the affected left knee in the future.

Discussion

Pigmented Villonodular Synovitis (PVNS) represents a benign, hyperplastic and proliferative synovial disease. It does not metastasize but can potentially be aggressive to the surrounding soft or

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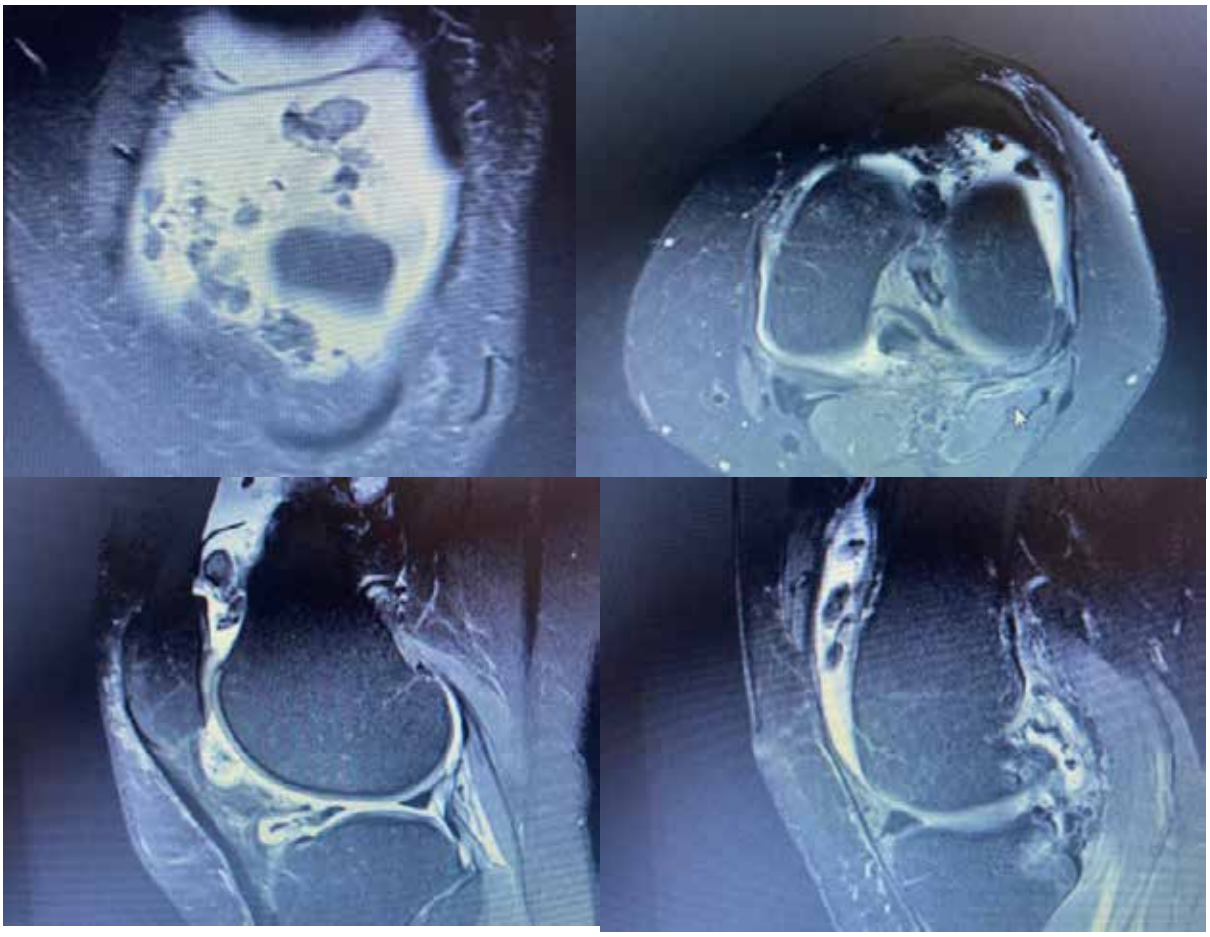

Figure 1. *MRI scan typically showed diffuse mass-like synovial proliferation with lobulated margins with low signal intensity due to hemosiderin deposition.*

TABLE 1.

The "safe treatment algorithm" followed for the management of knee diffuse PVNS in our hospital	
1. Clinical examination	• Symptomatology • Clinical signs • Synovial fluid aspiration
2. Imaging	• X-rays, MRI
3. Arthroscopy	• Synovectomy • Synovium biopsy for histological examination • Synovial fluid aspiration for cytological examination
4. Scintigraphy	• Tc^{99} three-phase bone scan
5. Radiohymenolysis	• Knee arthrogram for joint capsule integrity • $Yttrium^{90}$ administration for radiohymenolysis • Tc^{99} three-phase bone scan for Yttrium lekage
6. Rest	• 48 hours rest with Robert-Jones bandage
7. Follow up	• At 2 days for side effects • At 6 weeks, 6 months and 1 year for clinical manifestations of the involved joint

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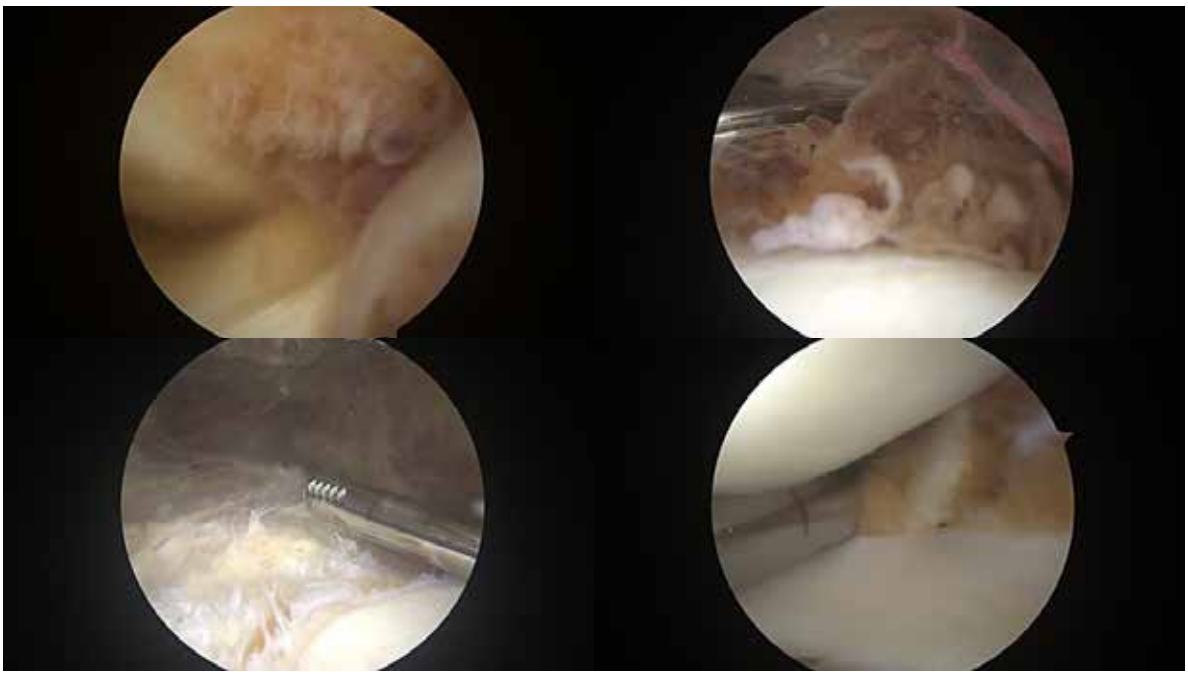

Figure 2. *Arthroscopy finding of DPVNS with brown colored lobulated hypertrophied synovium, before and after aggressive debridement.*

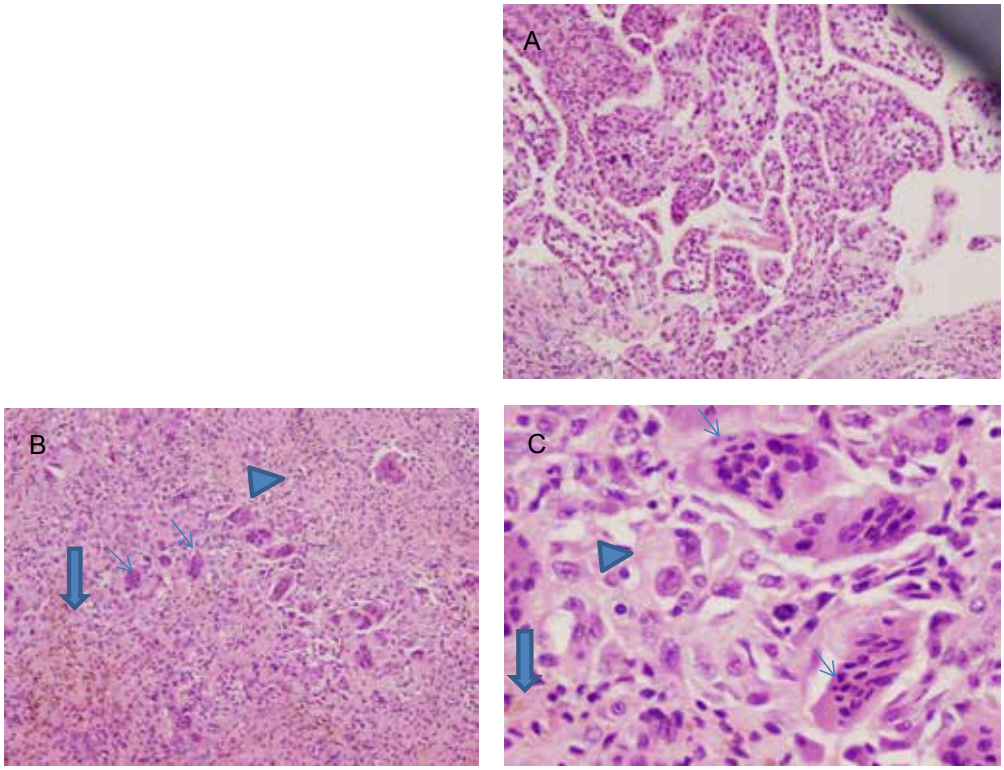

Figure 3. *Haematoxylin and Eosin staining x magnification histology specimens of the synovial membrane. (**A**) H&E X100 villous surface of the lesion. (**B**) H&E X100 osteoclastic-type giant cells (thin arrows), monocytoid cells (arrowhead), hemosiderin deposits (thick arrow). (**C**) H&E X200 osteoclastic-type giant cells (thin arrows), monocytoid cells (arrowhead), hemosiderin deposits (thick arrow).*

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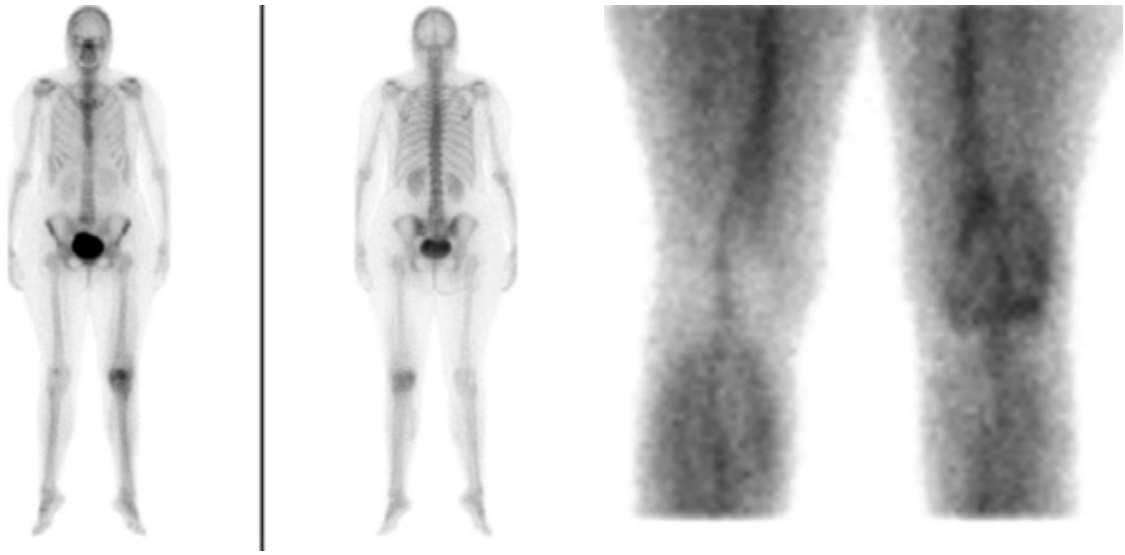

Figure 4. *Six weeks post-surgery a Tc-99m bone scan (blood pool phase) showed absence of any residual synovial reaction.*

bony tissues. When the tumor involves the tendons around the joint, or occurs in just one area of the joint, it is defined as Localized Pigment Villonodular Synovitis (LPVNS). When the condition is more widespread and involves an entire joint, the term Diffused Villonodular Synovitis (DPVNS) is used. The later, is also termed as Diffuse Type Tenosynovial Giant Cell Tumour in the most recent 5th edition of the WHO Soft Tissue and Bone Tumours classification.[1] It tends to be more aggressive and has increased recurrence rate and therefore, is more difficult to treat.

Young adults are mainly affected with the peak incidence observed between the second and fourth decade of life. The most frequently involved joint is the knee (28%-70%), followed by the hip, ankle, shoulder, and elbow joints.[2] The most common diffuse form has a reported recurrence rate up to 46%.[3] Microscopically, it is characterized by the presence of lipid-laden macrophages, multinucleated giant cells, hemosiderin deposits, and proliferation of fibroblasts and stromal cells. [4]

Because of its high local recurrence rate after surgery and the risk of osteochondral damage, there is growing interest towards novel therapeutic modalities that could be primary or adjuvant to surgical resection. The pattern of synovial gene and protein expressions in PVNS, similar to those in activated macrophages in rheumatoid arthritis, and the phenotype of multinucleated giant cells, characteristic of osteoclasts, suggest that there is a common autocrine mechanism in osteoclast differentiation in both diseases and indicate the potential utility of tumor necrosis factor (TNF)-alpha blockade. High synovial colony stimulating factor 1 (CSF1) messenger RNA (mRNA) expression in PVNS, unrelated to a chromosomal translocation involving CSF1 locus, may indicate that there is a synergic paracrine loop mediated by TNF-alpha and CSF1, as shown in both inflammatory and neoplastic conditions.[5] In 40 cases of PVNS, positivity of colony-stimulated factor 1 (CSF1), its receptor (CSF1R), and receptor activator of nuclear factor kappa-B ligand (RANKL) were immunohistochemically determined.[6] The relationship between the positivity and clinical outcomes was investigated. High positivity of CSF1 staining intensity was associated with an increased incidence of osteochondral lesions (bone erosion and osteoarthritis) ($p = 0.009$), but not with the rate of local recurrence. Positivity of CSF1R and RANKL

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staining was not associated with any clinical variables. The number of giant cells was not correlated with positivity of any of the three proteins, or with the clinical outcome. Particularly in knee cases, CSF1 positivity was also associated with the incidence of osteochondral change ($p=0.02$). CSF1R positivity was high in cases which had local recurrence, but not significantly so ($p=0.129$). It seems that determination of CSF1 and CSF1R expression may be useful as a prognosticator of the clinical course and/or outcomes of PVNS and especially of DPVNS. Additionally, the potential utility of tumor necrosis factor (TNF)-alpha blockade needs to be confirmed with larger controlled studies instead of rare reported cases in refractory PVNS.[7]

Arthroscopic synovectomy in DPVNS cases has gained popularity and seems to have several advantages over the open techniques especially in exclusively intra-articular cases.[8] In recent studies of arthroscopic synovectomy, the recurrence rate ranged from 16% to 50% at 5 years and up to 87% at 13 years. [9] Therefore, additional treatment options are deemed necessary to prevent local recurrence.

In the therapeutic algorithm of synovial disorders or persistent joint inflammation, radionuclide synovectomy or radiosynovectomy (RSV) with the use of radioactive agents is set between conservative treatment and operative procedures. In the case of pharmacotherapy failure, RSV is the radiopharmaceutical application of colloidal solution to joint cavities.[10,11] The most common indication for RSV is rheumatoid arthritis, although patients with seronegative spondyloarthropathies, unclassified arthritis, haemophilic arthropathy and other less common arthropathies such as pigmented villonodular synovitis benefit from this method.[12]

A commonly used radioactive agent for RSV is Yttrium-90 (^{90}Y). It is a colloid with 2.27 MeVw18x emitted β radiation with a natural half-life of 64 hours. Its maximum tissue penetration in the articular capsule and the adjacent cartilage is 11mm and 8.5 mm respectively. Regarding the mechanism of action, its diameter is small enough to be phagocytized, but big enough not to enter bloodstream via capillary fenestrations. After its intra-articular injection, ^{90}Y is phagocytized by type 2 synoviocytes (synovial macrophages) and captured in the external cell layers of the synovial membrane. The entrapped radioisotopes emit high energy β- radiation, which induces water hydrolysis, production of reactive oxygen species and cell apoptosis due to oxidative stress. With a half-life of 64 hours, ^{90}Y continuously emit radiation for a few weeks. In time, this leads to necrosis and subsequent fibrosis of the synovial membrane, a decrease in synovial fluid production and, clinically, reduction of inflammation symptoms. As mentioned, β- radiation has very limited tissue penetration, depositing more than 90% of energy within 10 mm from the point of origin, thus affecting almost exclusively the joint cavity. Most of the radiation is absorbed by the synovium, synovial fluid, superficial layers of cartilage and articular capsule. Subchondral bone and other para-articular tissues, in turn, receive negligible doses of radiation.[13]

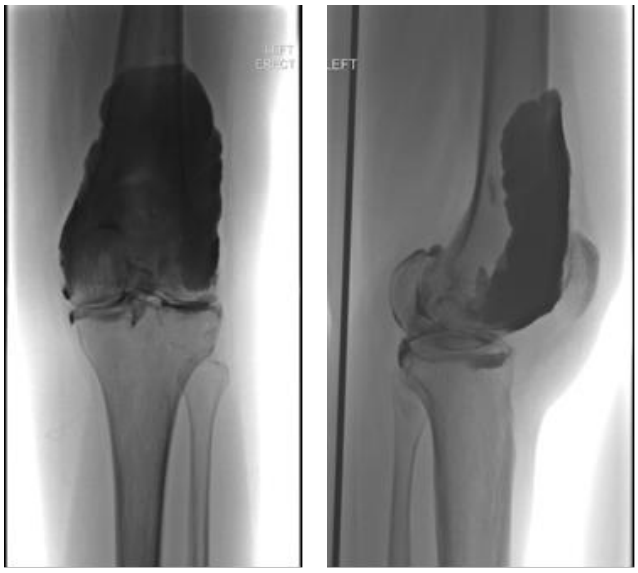

Figure 5. *Seven weeks post-surgery, arthrography of the affected knee before ^{90}Y administration ensured the integrity of the synovial capsule.*

^{90}Y intra-articular infiltration is used as adjuvant treatment along with the arthroscopic synovectomy in cases of PVNS in order to reduce the recurrence rates. Kollender et al, reported a 5% local recurrence rate in 20 patients treated with open or arthroscopic synovectomy followed by ^{90}Y admin-

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Figure 6. *PET scan, one hour after ^{90}Y administration, showed no leakage of the colloid into the extra-articular space.*

istration.[14] In a similar study by Oztemür et al, the recurrence rate was 0% over a follow-up period of 4.15 years.[15] Additionally, it seems that arthroscopic synovectomy in conjunction with ^{90}Y administration, increased patient-reported satisfaction rates.[16]

The safety profile of ^{90}Y is optimal as confirmed by direct post-administration scintigraphy. In a study of 30 cases, scintigraphy performed 24 hours post-^{90}Y administration, failed to identify any extra-articular leakage of the radiological agent. [3] In our case, we performed scintigraphy one hour after the radiotherapy for insurance cover reasons and for our patient's convenience.

In conclusion, meticulous arthroscopic synovectomy with adjuvant administration of ^{90}Y seems to be a safe method to prevent local recurrence in patients with PVNS. The adjuvant radio-synovectomy has no significant risks including environmental or extra-articular leakage. It is well tolerated by the patients with increased satisfaction rates and is also associated with decreased pain and improved joint function. Finally, it does not require hospitalization or prolonged rehabilitation.

It is necessary to mention that RSV is not a *panacea* and its therapeutic effects are considerably worse in patients with co-existent osteoarthritis and advanced joint degeneration. Therefore, meticulous patient selection is strongly recommended.

Despite its advantages, radionuclide synovectomy is not routinely used at present. Therefore, additional studies are necessary to assess the long-term efficacy of ^{90}Y adjunct treatment in controlling the recurrence rate of PVNS. There are no large series with long-term follow-up and a meta-analysis is still missing for safer conclusions. Regarding pharmaceutical targets, in the light of recent observations, CSF1/CSF1R interaction probably represents a more sensible therapeutic target than TNF-alpha blockade in the diffuse form of PVNS.[17]

The authors declared no conflicts of interest.

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Spinal cord injury and Sexual health

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ABSTRACT

The estimated global incidence of spinal cord injuries is 10.5 cases per 100.000 people. Apart from the motor and sensory damage, spinal cord injuries affect the patients' sexual function and sexual activities. Arousal, erectile function, orgasm and fertility are the main somatic factors that are affected by the spinal cord injury. In addition, spinal cord injury patients show a higher rate of body image issues as well as psychological issues (anxiety, depression, post-traumatic stress disorders) which interfere with their sexual activities and lower their sexual satisfaction. Since there is no cure for spinal cord injury, therapeutic approaches related to the rehabilitation of sexual function mainly focuses on restoration of "normal" function. Pharmacological treatments and intracavernous injections for erectile dysfunction, body-exploration, assistive devices and sexual aids are some of the methods that healthcare professionals and patients can explore in order to improve sexual function and sexual satisfaction post-injury.

Key Words: Spinal cord injury, Sexual function, Sexual satisfaction, Sexual Health, Sexual dysfunction

Introduction

The term spinal cord injury (SCI) refers to any impairment of the spinal cord as a result of trauma, disease, degeneration or neoplasm. The estimated global incidence of traumatic spinal cord injuries is 10.5 cases per 100.000 people which leads to an annual number of incidences close to 768.473. Road traffic accidents and falls are the most common mechanisms of traumatic SCI and the number of incidences appears higher in countries with low and average income [1]. SCI affects the motor and sensory signal conduction across the site of the lesion as well as the autonomic nervous system. Injuries are classified as incomplete when there is sacral sparing (presence of motor and sensory function in the most caudal sacral segments) or complete (absence of sacral sparing) [2]. Apart from the damage on the motor and sensory function (extend of which depends on the level and the severity of the injury), the autonomic nervous system is also affected. Hemodynamic disorders, neurogenic bladder and bowel as well as sexual dysfunction are common impairments following SCI [3].

In able-bodied men arousal, ejaculation and orgasms are controlled by the sympathetic and parasympathetic nervous systems. Psychogenic erections and seminal emission are controlled by the T11-L2 sympathetic outflow, while reflexogenic erections are controlled by the S2-S4 parasympathetic outflow. In able-bodied women the sympathetic nerve fibers located at the thoracolumbar section are re-

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The process of identification and the criteria of inclusion-exclusion are described on the following flowchart (Table 1).

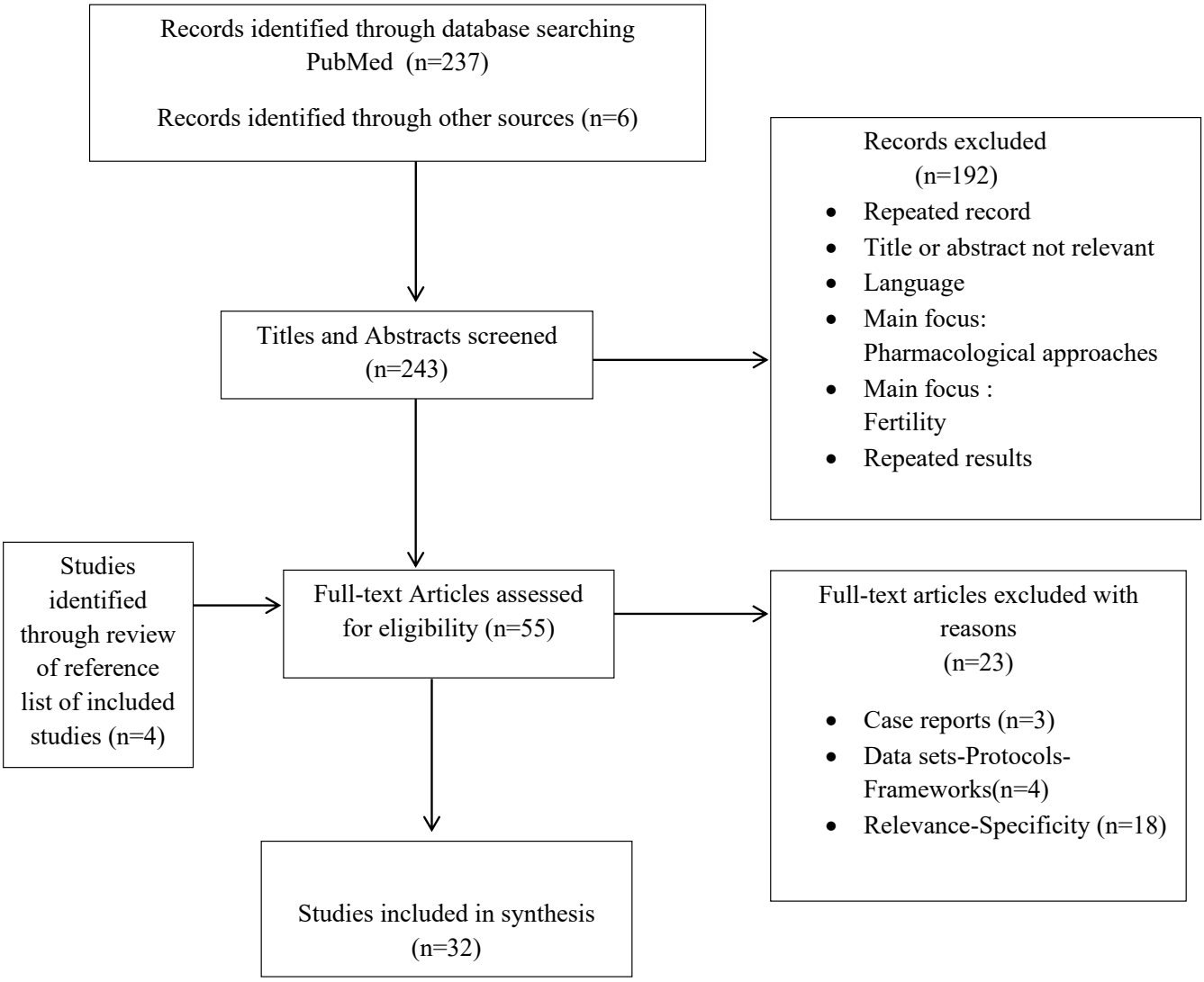

Table 1: Flowchart

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sponsible for psychogenic sexual arousal that leads to vaginal lubrication and clitoral enlargement, while reflexive sexual arousal is mediated by the nerve fibers of the pudendal nerve (S2-S4) and by the S2-S4 parasympathetic efferents [4]. Regarding orgasms in able-bodied men, orgasm is experienced as the result of cerebral processing of sensory information by the pudendal nerve which is caused by an increase of pressure in the posterior urethra [5], while able-bodied women experience orgasm as a variation of a transient sense of intense pleasure that creates an alternate state of consciousness and is accompanied by involuntary rhythmic spasms of the pelvic floor muscles combined with urethral and anal spasms and myotonia that completes the sexually induced vasoconstriction [6].

The current working definition of sexual health according to the World health organization is useful in better understanding the impact of SCI and is as follows: "A state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled" [7].

According to Alavinia *et al*, sexual health constitutes a high priority area of rehabilitation for SCI patients [8]. For this reason, a review of the current literature was performed to identify ways that SCI interferes with patients' sexual health, function and satisfaction as well as the interventions that are being utilized in order to help patients achieve a better quality of sexual life. Pubmed database was used to identify studies, reviews and articles regarding the sexual health in people with SCI.

The key words "spinal cord injury", "sexual function", "sexual dysfunction", "sexual health", "sexual rehabilitation" and "impact" were used. Search parameters were specific regarding date of publication (from 2000 until 2020) and relevance. The process of identification and the criteria of inclusion-exclusion are described on the following flowchart (Table 1).

Discussion

The relationship between SCI and sexual health is being investigated for some years now. The impact that the injury has on the sexual health, function and satisfaction of patients depends on the age of the patient, the mechanism of injury (injuries that are caused by falls from heights have a more severe impact on the patients sexual life) as well as on the patient's goals and future aspirations. In a study by Taylan et al, patients with ASIA D classification reported lower levels of impact in the avoidance and impotence sub-section of the GRISS questionnaire while patients with ASIA A and B classification reported lower level of impact in the frequency, satisfaction, touching, anorgasmia and premature ejaculation sub-dimensions of GRISS [9]. Generally, the impact of SCI on patients' sexual function depends on the level and type of injury (complete or incomplete).

In men, the ability for reflexogenic, psychogenic and nocturnal erections is related to the level of the injury, the severity and type as well as the stage of injury and of the rehabilitation process [10]. More specific, reflex erections are more common in injuries above the L3-L4 level (given that the erection spinal reflex is intact) while psychogenic erections are more common in men where the level of injury is below the lumbar and sacral spinal regions and less common when the level of injury is at or above the T9 level and "co-exists" with disruption of the sympathetic flow [11]. Ejaculation follows a similar pattern and is more common in men with incomplete spinal cord injuries, while in men with upper motor neuron impairment the sexual stimuli are not enough to activate the spinal reflex arc of ejaculation [10]. There is also a high chance of entry disturbance of the sperm in the posterior urethra and a disruption in seminal expulsion (through the penile urethra and urethra orifice) which creates fertility problems to men with spinal cord injury [10].

Additionally, another aspect of sexual health and sexuality that is impaired is the ability to experience orgasms. Men with spinal cord injury have reported spasms, shivers, feelings of satisfaction and of impending ejaculation when asked to describe their orgasm experiences [12], while a study by Soler et al showed that men who can achieve anti-retrograde ejaculations had a higher chance of experiencing orgasms in com-

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parison to men who achieved reflex ejaculations [13].

The impact of SCI in women's sexual function is similar, with vaginal lubrication and vaginal blood flow being the main affected factors. The sympathetic cell bodies at the T11-L2 level control vaginal blood flow and the presence of an intact sacral spinal arc combined with a regulated psychogenic arousal are needed for sexual arousal and vaginal lubrication. Women with SCI experience higher levels of sexual distress and lack of vaginal lubrication compared to able-bodied women [14]. In addition, urinary and bowel incontinence, spasticity and autonomic dysreflexia result in higher levels of anxiety and lower levels of sexual satisfaction [15]. Orgasms are described as "harder to achieve" and lower in quality compared to pre-injury experiences [16]. In a study by Kreuter et al, regarding the experience of orgasm in 234 women with SCI, 8% reported no change in the quality of orgasm after injury, 25% reported pleasant and satisfactory feelings , 31% reported a feeling of relaxation, 3% reported unpleasant feelings and only 8% reported lack of orgasms after the injury [17]. Another aspect of the symptoms of the SCI that interfere with patients' sexual function is autonomic dysreflexia (AD). In patients with injuries at or above the T6 level, different sexual activities (with ejaculation being on the top of the list) have a higher chance of producing an AD episode. According to Courtois et al, a way to inhibit the appearance (or the effect) of AD is the use of nifedipine as a prophylactic and acute intervention [18].

It is worth remembering that the mental state of a person greatly affects his or her sexual life. Patients with SCI show higher levels of dysphoria and lower levels of satisfaction in comparison to healthy population. They also have a higher chance of developing depression, anxiety and post-traumatic stress disorders [19]. The psychological aspects of the injury can sometimes have a greater impact on patients' sexual adjustment post injury than the physical aspects [20]. The perceptual, cognitive, affective and behavioral dimensions of body image are also affected by SCI, according to a pilot study by Bailey et al. Besides that, the participants reported a strong need to be viewed as "normal" [21]. In addition, there are changes in patients' sentimental life following SCI. The most significant predictor regarding the quality of sentimental life, besides the overall quality of life, is the ability to drive a vehicle. It's not surprising that driving a vehicle grants a higher level of independence and can help a person seek a more active social life and engage in interpersonal relationships [22].

Interventions

As mentioned, sexual health is a high priority in terms of rehabilitation for people with spinal cord injuries. Before discussing the different types of interventions, it is important to highlight the role of healthcare professionals in the rehabilitation of patients' sexual function. New et al, conducted a study in a group of 175 people with traumatic and non-traumatic spinal cord injuries to record and compare their experiences regarding sexual education (as part of the rehabilitation process) as well as their preferred methods of delivery of this kind of information. Interestingly, people with non-traumatic spinal cord injuries ("spinal cord disease") were less likely to receive sexual education as part of the rehabilitation process. The preferred methods of information delivery were sexuality counselors, internet sites, peer support workers, staff discussions, DVDs, and written information. Based on their results, New et al, proposed a list of subjects that healthcare professionals should be able to discuss with their patients such as contraception, safe sex practice, sexually transmitted infections, self-esteem training, erogenous zones and options regarding non-intercourse sexual activity [23]. Regardless of the way and the medium that a healthcare professional chooses to discuss these subjects, the most important thing is to maintain respect for the patient's believes and needs. Sexuality is an intricate subject with a "heavy" psychological background. Phrases like "abandon sex", "sex is dead", "give it time" can do more harm especially in cases where patients have not received the necessary information regarding their sexual function and their sexual options post-injury. Every healthcare professional should possess the ability and basic knowledge to answer patients' questions regarding sexual function and activity and/or refer them to a specialist [24].

Starting with the pharmacological options, the use of phosphodiesterase type 5 inhibitors (pde5i) is considered the first line of treatment for managing erec-

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tile dysfunction. In men with SCI, pde5i drugs like Sildenafil, Vardenafil and Tadalafil improve erectile function as well as the overall sexual life quality due to their tolerance and ease of use. Soler et al, assessed the efficacy of ped5i in erectile dysfunction in 240 patients with SCI. 120 patients were on Sildenafil (Viagra), 54 patients were on Tadalafil (Cialis) and 66 patients were on Vardenafil (Levitra). 85% of patients on Sildenafil, 74% of patients on Vardenafil and 72% patients on Tadalafil reported improvement in penile rigidity ("enough for penetration"). It is important to note that according to Shridharani et al, in men with cervical or high thoracic injuries the use of pde5i can lead to dizziness. Furthermore, on the subject of ped5i use in SCI patients Alexander et al, in a double-blind placebo control flexible dose study assessed the efficacy, safety and tolerability of per os Sildenafil in 129 women with sexual arousal disorder due to SCI. They reported a similar improvement in sexual activity in both the active and placebo group noting the absence of clinical relevance of Sildenafil in women with spinal cord injury [25-27]. In cases where the use of per os ped5i drugs is not well tolerated or effective, administration of intracavernous injections is another option that physicians and patients can explore. In a systematic review and meta-analysis of 283 studies involving 713 patients with SCI Chochina et al, reviewed the efficacy of intracavernous injections and reported that in 88% of the population intracavernous injections led to successful erections using either a combination of papaverine and phentolamine, papaverine alone or alprostadil [28].

In terms of non-pharmacological and non-invasive approaches there are some data that indicate that the use of vacuum devices and/or restrictive rings can improve erections under the right circumstances (intact reflex arc) in combination with other treatments [29]. Focal vibrations are also a non-invasive option that men with incomplete SCI can explore. According to a study performed by Calabrò et al, the use of focal vibrations in the pelvic floor (using a pneumatic vibrator) in 10 men with incomplete SCI (ASIA C-D) resulted in improvements on the IIEF (international index of erectile function) and MAS (modified Asworth scale) scores, improved cremasteric and bulbocavernosus reflex responses as well as an increase in the pudendal somatosensory evoked potential and in the electorophysiological bulbocavernosus reflex. The authors also noted that muscle vibration can lead to reduced spasticity and improved muscle synergies through both bottom-up (reset of sensimotor hyperexcitability from sensory inputs) and top-down mechanisms [30].

On the subject of ejaculation and orgasms, the two most well-known methods are penile vibration stimulation (PVS) and electo-ejaculation (EEJ) which also facilitate sperm retrieval for fertility purposes. In 2010, Bracket et al published their results after evaluating 3152 sperm extraction interventions from 500 different men with SCI and noted a 54% success rate when using the PVS method (in 461 patients) and a 91,9% success rate when using the EEJ method (in 210 patients) [31].

Moving on to more invasive and surgical interventions that aim to restore sexual function in men with SCI, penile prosthesis is the oldest and perhaps the most known procedure that aims to restore erectile function in men with SCI, although it carries a fair amount of risks and complications (mainly due to corrosion of the device and infections) [32]. Another invasive approach that can be explored by men is sacral neuromodulation, a procedure that was first introduced for the management and rehabilitation of neurogenic bladder. A neurostimulator that is implanted through the S3 foramen sends an electrical pulse to the sacral plexus resulting in improved erections. In a study by Lombardi et al, 52 men suffering from lower urinary tract symptoms and concomitant erectile impairment were selected and evaluated for sacral neuromodulation (29 out of 52 patients had neurogenic erectile impairments including incomplete SCI patients). The authors reported a clinical improvement and maintenance of improved erectile function in 35.7% of the neurogenic subjects [33]. For men with injuries below the L2-level there is also the option of the TOMAX procedure which involves a microsurgical connection of the sensory ilioinguinal nerve to the dorsal nerve of the penis unilaterally and aims at restoring tactile and erogenous sensitivity in the penile glans. In 2012, Overgoor et al published their results after performing the TOMAX procedure in 30 patients with no penile sensation but good groin sensation (Spinal bifida: 18 patients, Spinal cord injury: 12 patients). The authors

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noted an 80% improvement in unilateral penile glans sensation leading to improvements in urinary continence, independence, and sexual life [34].

Regarding the restoration and rehabilitation of sexual function and sexual health in women with SCI, the first step is encouraging the exploration of different methods of stimulation (beyond clitoral stimulation) such as stimulation of the vagina (G-spot) and stimulation of the cervix and the nipples [35]. Vibratory stimulation devices (VS) as well as clitoral vacuum suction devices (CVS) have shown great results in facilitating orgasms. According to Alexander et al, in a population of 23 women with orgasmic dysfunction (18 with multiple sclerosis and 5 with SCI) both methods are safe and effective with the difference that CVS results in an overall improvement of the sexual function (which was maintained for 4 weeks after treatment) whereas VS results in improvements only in orgasms and only during active treatment [36]. Finally, in a recent study Zimmerman et al, reported increase in vaginal blood flow in lab-rats supporting the already proposed theory that tibia nerve stimulation can be considered as an alternative approach in the rehabilitation of sexual arousal disorders in women [37].

Regardless of the person's anatomy and chromosomes, everyone should be encouraged to explore their body, different positions and sexual aids/devices in order to maximize sexual satisfaction. One of the most inclusive and educational manuscripts (for patients and medical professionals) regarding the sexual activity and sexual life of patients with disabilities is the "Pleasure-able: Sexual device manual for persons with disabilities" by Krassioukov et al. It addresses matters such as anatomy, safety, lubrication, positioning, lubrication, sexual aids etc. while being sex positive and inclusive to persons of all abilities, genders, age, race and sexual orientation [38].

Conclusion

The impact of SCI in a patient's life is not determined only by the motor and sensory impairment. Sexual function is also affected (directly or indirectly) and can sometimes have a greater impact in a patient's quality of life. Men encounter difficulties in achieving and/or maintaining erections and orgasms while women encounter difficulties due to lack of vaginal lubrication and lack of vaginal blood-flow. Regardless of the patient's sex, the psychological effects of the injury indirectly affect their sexual function, health, satisfaction and their sexuality. Depression, anxiety, sexual distress, and body-image issues have a higher prevalence in people with SCI and lead to lower self-esteem and lower satisfaction in sexual and sentimental life. Healthcare professionals should be ready to educate and address patients' concerns regarding sex, orgasms, and fertility and either help in creating a rehabilitation protocol (that fits patient's needs) or refer them to a specialist. With the use of pde5i drugs (Sildenafil, Vardenafil or Tadalafil per os or via intracavernous injections) in combination with body-exploration, sexual aids and devices (vacuum devices, vibrators, restrictive rings) and different positions or with the use of more invasive approaches (like the TOMAX procedure or sacral neuromodulation) a patient's sexual life can really be improved. It is important to keep in mind that every person requires a different approach and moves in a different pace. Further studies regarding the impact of SCI in sexual health and sexuality as well as the possible interventions (for example the potential use of electric nerve stimulation) are needed in order to further improve the overall quality of life of people with SCI.

Conflict of interest

The authors declare no conflicts of interest.

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Botox applications in patients with neurological symptoms following Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) is defined as damage to the spinal cord causing temporary or permanent changes in patient's major functions. The main type of SCI occurs from direct trauma, as in accidents, and is called traumatic. Despite scientific and therapeutic progress, traumatic SCI remains a major cause of morbidity and mortality. Its long-term medical complications have serious consequences for patients and their families; therefore, finding effective therapeutic interventions is very important. This study is a review of the existing literature on the therapeutic effects of botulinum toxin (Botox) as an intervention for the treatment of neurological complications occurring in patients after SCI, with emphasis on chronic complications. Botox is produced by the bacterium Clostridium botulinum, which causes botulism in humans. There are seven immunogenic toxins, however, the most used formula is BoNT-A. Botox treatment in patients with SCI is effective against spasticity, bladder dysfunction and chronic pain.

Key Words: Spinal Cord Injury, Botox, Spasticity, Urinary system, Pain

Introduction

Spinal cord injury (SCI) is defined as damage to the spinal cord causing temporary or permanent changes in patients' main functions as various degrees of motor and/or sensory deficits, paralysis, paraplegia, and quadriplegia [1,2].

Based on the etiology, SCI can be categorized into traumatic and non-traumatic. Traumatic SCI can occur from external physical factors that directly damage the spinal cord as in car accidents, falls and injuries during sports activities or cases of violence. Non-traumatic SCI is caused by an acute or chronic disease, such as tumor or infection [3].

Traumatic SCI occurs more often in men (79.8%) than in women (20.2%). Regarding the age profile, people with traumatic SCI are mainly between 15-29 years old [3]. Despite scientific and therapeutic progress, traumatic SCI remains a major cause of morbidity and mortality. Acute hospital mortality is estimated to range from 4% to 17%, while post-discharge annual mortality rates remain consistently high [1].

The pathophysiology of SCI is classified into two phases of injury, the "primary" and the "secondary". "Primary injury" results from direct physical injury to the spinal cord, where cell lysis begins. Then, a complex process of "secondary injury" takes place, which through a cyclical process promotes neuronal and glial cell death, causing inflammation. "Secondary injury"

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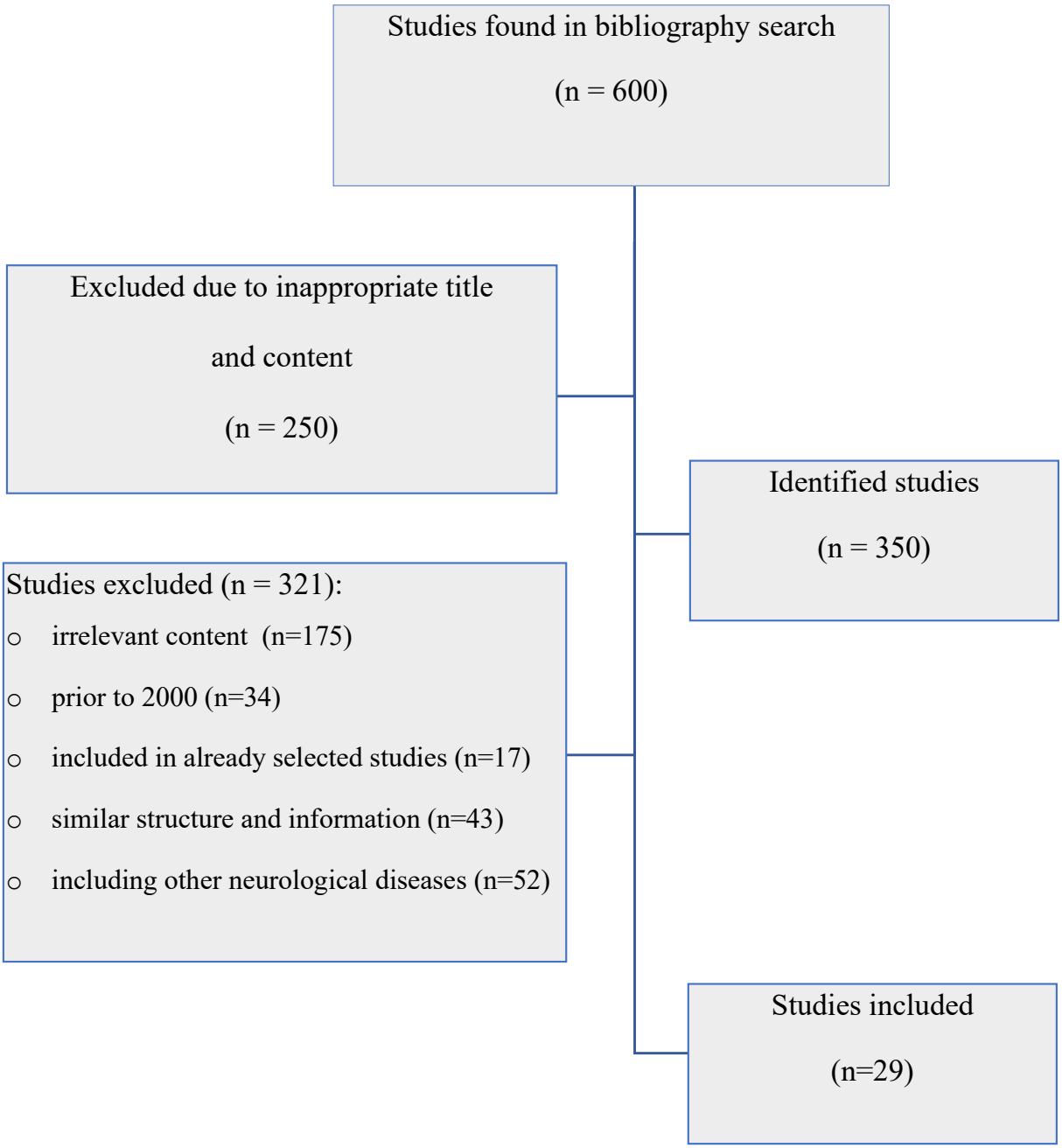

Figure 1: Flowchart

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is divided into the following phases: (i) acute (<48 hours), (ii) subacute (48 hours to 14 days), (iii) intermediate (14 days to 6 months) and (v) chronic (> 6 months) phases [1,3].

A serious condition like this entails long-term medical complications, which have devastating consequences, physical, social, as well as occupational, for the patients and their families. The main features are loss of independence, increased rates of hospitalization and mortality, loss of employability and quality of life [2,4]. Chronic complications of SCI vary and include musculoskeletal, respiratory, cardiovascular, gastrointestinal and urinary disorders, as well as spasticity and chronic pain. Musculoskeletal complications include "Charcot" neuropathic arthropathy, osteoporosis, and bone fractures [3,4]. Respiratory complications, mainly respiratory failure, are the most important cause of morbidity and mortality both in the acute and in the chronic phase. Cardiovascular complications include orthostatic hypotension, autonomic dysreflexia, and thromboembolism [4]. Gastrointestinal and urinary tract disorders, such as neurogenic bladder and neurogenic bowel, are a significant source of social and psychological stress for patients with SCI [1,4]. Incontinence, kidney failure, and urinary tract infection are some of the complications of this condition [5]. Spasticity is a common secondary complication of SCI, resulting from injury to the upper motor neurons in the central nervous system, and is characterized by hypertension, intermittent or prolonged involuntary physical reflexes (hyperreflexia), clone and muscle spasms [6]. Spasticity affects 70% of patients with SCI and causes significant disability in many patients [4]. Chronic pain is distinguished to algebraic (musculoskeletal) and neuropathic pain, and is one of the common secondary complications, affecting up to 80% of patients with SCI [7]. It is therefore understandable that patients with SCI display significant acute and chronic complications, which negatively affect their functional independence and quality of life. The development of effective therapeutic approaches, aiming at the improvement of patients' functional level and quality of life, as well as in reducing secondary morbidity is becoming extremely important [3,4].

Clinical applications of Botox have proven to be a useful tool for managing different complications following SCI, such as spasticity, chronic pain and bladder dysfunction. Botulinum toxin (BoNT) is one of the most potent natural neurotoxins, which has emerged in recent decades [8,9]. This study is a review of the applications of Botox as a therapeutic tool for the rehabilitation of long-term complications in patients with SCI. The research for the suitable literature took place using the Google Scholar database, where 600 articles were initially collected, and then were limited to 29 as they were considered more appropriate for the present study (Figure 1).

Discussion

Botulinum toxin (BoNT) is a neurotoxin produced by the anaerobic bacterium Clostridium botulinum and is one of the most poisonous substances that causes botulism in humans. Botox is characterized by four genetic groups with seven different immunogenic toxins (A - G), which are produced during the formation of spores of Clostridium Botulinum [10]. Types A, B and E are more commonly involved in cases of botulism in humans, while types A (BoNT-A) and B have been used with clinically beneficial effects in various neurological disorders and are available for treatment. Although types A and B are available in medicine, the most used type is BoNT-A [11].

Chemical structure and Mechanism of action of Botox

The toxins have a molecular weight of ≈ 150 kDa, and despite having many serotypes, all BoNTs have structurally similar characteristics, consisting of two chains linked by a disulfide bond: a light chain and a heavy chain [12]. The light chain is the toxic unit, while the heavy chain provides protection to the molecule from digestive enzymes, allowing the bacterium to act as a food poison [10]. The heavy chain of BoNT binds to the vesicular synaptic protein (SV2) and enters the presynaptic end of the nerve cell via endocytosis. The disulfide bond then breaks down, and the light chain that is now the active part of the molecule breaks down a protein called SNAP-25 in the presynaptic membrane. Subsequently, the fusion of acetylcholine-containing vesicles into the plasma membrane is stopped [9]. As a result, the release of acetylcholine is inhibited, causing the affected neuromuscular con-

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nections to become paralyzed and the muscle contraction to decrease. Clinical effects occur 24-72 hours after injection, while the reason for this delay is unknown [10]. BoNT-A inhibits the release of acetylcholine and other neurotransmitters into the neuromuscular junction in human striated muscle. Intravesical administration of BoNT-A results in the cleavage of SNAP-25, inhibiting the release of vesicular noradrenaline and preventing the activation of α- and β3-adrenoceptors. This affects the contraction of the bladder and allows the detrusor to relax [9].

BoNT-A applications in SCI

Spasticity

Spasticity is a common complication of SCI that can significantly increase dysfunction, as spastic involuntary muscle contraction competes with voluntary muscle action, and as a result function is inhibited. This can cause pain and lead to contractions, reduced mobility and cause various problems in patient's daily activities [13]. Botox has been reported to inhibit the release of acetylcholine from the nerve cell end. Botox, when injected intramuscularly, spreads approximately 30 mm through muscle and fascia, binding presynaptic cholinergic nerve cells [14]. The reduction of muscle fiber contraction begins in 24 to 72 hours after administration, while the maximum effect is observed in 5 to 14 days. The duration of its action varies from 2 to 6 months depending on the dosage [15]. By injecting BoNT-A into certain muscles, local muscle hyperactivity can be reduced without affecting other muscles, thus improving function, and preventing deformities, so its use is indicated in local spasticity [16]. The treatment is effective in reducing pain and muscle spasm. The main side effect is the excessive weakness of the treated muscle [6]. It may be necessary to locate specific muscles with electromyographic guidance to produce optimal results [13]. Palazón-García *et al*, studied the effect of BoNT-A in 90 patients with SCI. The authors reported a significant improvement in muscle tone, increased range of motion, and reduced pain, with no adverse side effects. Patients with the slightest injury showed greater improvement. In addition, significantly greater improvement in muscle tone was observed in patients with local spasticity and with immediate administration of BoNT-A after injury [16]. In another study, Ma *et al*, injected BoNT-A into rats to investigate the inhibition of muscle spasticity by blocking calcium channels. The results showed that Botox may reduce SCI-induced muscle spasticity by affecting the expression of the Cav3.2 calcium channel subunit in rats [17]. In a different study, Marciniak, Rader, & Gagnon injected BoNT-A into 28 adults, showing 56% improvement in movement, 71% improvement in maintenance of positioning, 78% improvement in upper limb function, and 83.3% reduction in pain. BoNT-A appeared to be an effective treatment for reducing local spasticity and increasing function in patients with SCI [18]. In a similar study, Opara, Hordyńska, & Swoboda administered BoNT-A infusion to 20 paraplegic patients with SCI with moderate to severe lower extremity spasticity. The injection was given in the thigh adductors and knee and leg flexors. There was improvement in most patients who experienced reduction or relief of pain [19].

Urinary system

The most common urological complications in SCI are urinary tract infection and bladder dysfunction [5]. Bladder dysfunction is associated with overactivity of the detrusor [11]. People with an overactive bladder often complain of one or more of the following problems: incontinence, frequent urination and nocturia. The neurogenic hyperactive detrusor is used to describe a urodynamic finding characterized by involuntary contractions of the detrusor during the filling phase [20].

The exact way that Botox affects the bladder is still unclear. According to initial findings, relaxation of the detrusor was observed [10]. Injection of BoNT-A to the detrusor has been found to affect the adrenergic nerves and sensory fibers, blocking the presynaptic release of acetylcholine from the parasympathetic active nerve, promoting paralysis of the motor neurons of the bladder, similar to the way it acts on the striated muscle [12,20]. Kuo studied the effect of BoNT-A in patients with SCI, who had difficulty in urinating and incontinence, by injection into the urethral sphincter and into the detrusor, respectively. Urodynamic parameters showed significant improvement in both groups, with better results in patients injected into the detrusor. However, a discrepancy was observed between

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the objective urodynamic results and actual patient satisfaction [21]. In another study, Chen, Chang & Kuo investigated changes in proteins of urothelial connection and suburothelial inflammation before and after BoNT-A injection into the detrusor in 26 patients with SCI. Urinary dysfunction and protein concentrations in patients' bladders were recovered after treatment with BoNT-A. However, this effect decreased over time [22]. Chen, Xie, & Jiang investigated the efficiency of BoNT-A injections at the detrusor in patients with urinary incontinence and bladder compliance secondary to SCI. The duration of the study was 12 weeks, where a significant reduction in cystourethral regression was observed, incontinence was improved as the pressure exerted on the bladder decreased, and urine volume increased [23]. Chen *et al*, applied directed peripheral BoNT-A infusion to 18 SCI patients in the external urethral sphincter to treat external sphincter detrusor dysfunction. The followings were observed: a) significant reduction in static urethral pressure and bladder contractions, b) significant reduction in urine residues, in the first and second months after treatment, c) contractions and pressure exerted on the detrusor did not decrease sufficiently [24]. Jia *et al*, investigated the effect of BoNT-A on urinary tract infection in 41 men with neurogenic extrinsic hyperactivity following SCI. The study lasted 6 months and the injection was performed in the detrusor. BoNT-A significantly reduced urinary tract infection, possibly associated with decreased urine residues and decreased detrusor contractions [25].

Neuropathic Pain

Pain is one of the most common SCI complications, with pain prevalence rates ranging between 75% and 81%. The most common subtype of chronic pain in SCI patients is neuropathic pain, which is defined as "pain caused by a damage or disease of the somatosensory system" [8, 26].

Although BoNT-A is commonly used to treat spasticity and urinary tract complications, studies have shown that it is effective in treating chronic pain conditions such as chronic migraine, mesothermal neuralgia, post-traumatic neuralgia or diabetic neuropathy [27]. It has been suggested that BoNT-A may inhibit neurogenic inflammation and peripheral sensitization of nicotine fibers by inhibiting the release of local neuropeptides, thereby reducing pain [26]. Li *et al*, studied the effect of Botox against neuropathic pain in 44 patients with SCI who were divided into two groups. In one group BoNT-A was injected into the area of pain, while in the second group placebo (saline solution) was injected. Individuals in both groups were treated daily for 8 weeks. BoNT-A intervention was more effective than placebo in significantly reducing neuropathic pain in patients with SCI [28]. In a similar study, Han *et al*, studied the analgesic effect of BoNT-A on neuropathic pain in 40 patients with SCI. The study lasted 8 weeks with patients divided into two groups, where one group received placebo and the other group was injected with BoNT-A. Among the participants in the BoNT-A group, 55% reported pain relief of 20% or more, while in the placebo group only 10-15% reported a similar level of pain relief [29].

In conclusion, SCI remains a serious medical condition that causes acute and long-term secondary medical complications. Patients' autonomy and quality of life are adversely affected by chronic complications, which is why early prevention and treatment are essential. The use of BoNT-A as a therapeutic intervention is applied to chronic complications, such as spasticity, urinary tract disorders and neuropathic pain. Its mechanism of action and its effectiveness in reducing spasticity have been adequately studied and the findings suggest that reducing muscle spasms significantly increases patients' range of motion. The findings from the application of BoNT-A in the urinary system are positive, although its mechanism of action is still under study. Regarding the application of Botox to reduce neuropathic pain, which is a relatively new subject of study, the results are optimistic. However, the mechanism of action has also not yet been clarified. Further studies regarding the use of Botox in patients with traumatic SCI and its mechanism of action are needed to improve its clinical outcome and improve patients' quality of life.

Conflict of interest

The authors declare no conflicts of interest.

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Feeding disorders and nutritional needs in patients with spinal cord injuries

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ABSTRACT

Poor nutrition in spinal cord injury (SCI) patients can lead to medical complications such as skin ulcers, osteoporosis, obesity, diabetes, dyslipidemia, neurogenic problems of the intestine and bladder and fitness issues that can affect mobility and functional independence. The aim of this study was to review feeding disorders and nutritional needs in patients with SCI. For this reason, a review of the current literature was performed by using the online PUBMED database and the following keywords: "spinal cord injuries" AND ("diet" OR "nutrition" OR "malnutrition" OR "feeding" OR "eating disorders" OR "nutritional needs"). The search retrieved a total of 509 papers. After screening of titles and abstracts, 426 articles were rejected as irrelevant with the topic. Of the 83 remaining publications evaluated, 43 were rejected for various reasons. After reviewing the reference lists of the remaining studies, 6 more studies were identified. Finally, 46 studies were included in the present review. Patients with SCI are disabled for life and must change their lifestyle greatly. Injuries in cervical spine may compromise the process of swallowing, causing dysphagia and respiratory complications. The risk of under-nutrition and malnutrition in SCI patients is high. Poor diet negatively affects overall health leading to obesity, cardiovascular disease, diabetes mellitus and metabolic syndromes. Patients with SCI must follow a proper diet to ensure that the right amount of nutrients is delivered for sustaining the appropriate physiological mechanisms.

Key Words: Nutritional needs, Spinal Cord Injuries

Introduction

Spinal cord injury (SCI) affects the ability of the spinal cord to control motor, sensory and autonomic functions below the level of injury. A complete SCI results in loss of sensation and motion below the level of the injury, however, in cases of incomplete lesions, part of the mobility or sensation continues to exist [1]. SCI is less common than brain injuries, having an annual incidence of up to 40 cases/100,000 people, and most frequently affects young people. The main cause of SCI is traffic accidents, followed by sports injuries and occupational accidents. In case of injury, the spinal cord responds similarly to the brain. Bleeding, hematoma formation and neuronal damage is followed by a long phase of recovery [2]. Although SCI is usually located at a certain site, it affects the entire body area innervated by nerves deriving from the site of injury. Morbidity and mortality of patients

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with SCI has improved significantly in recent years due to the great progress that has been made in the provision of first aid [3].

Following serious SCI, there is high probability that patients will suffer from nutritional insufficiency, despite recent advances in medicine and nutrition science. In the immediate post-traumatic period, the metabolic needs of SCI patients are considered similar to those of patients with traumatic brain injuries. Research has shown that 40% to 50% of hospitalized SCI patients are at high risk of malnutrition, while up to 12% of patients are severely malnourished [4]. Poor nutrition can lead to medical complications such as skin ulcers, osteoporosis, obesity, diabetes, dyslipidemia, neurogenic problems of the intestine and bladder and fitness issues that can affect mobility and functional independence [5]. In contrast, a healthy diet rich in nutrients can help provide energy and boost the immune system, helping patients rehabilitate and live a more productive life [6].

Focusing on diet and fluid intake is crucial for SCI patients, as many of the observed complications such as infections of the urinary and respiratory tract are exacerbated by weight loss and dehydration [7]. On the other hand, it is possible for patients with SCI to have a lower metabolic rate due to denervated muscles. This means that some patients may need to decrease food consumption, as the body needs fewer calories to burn [8]. Maintaining an ideal weight and a proper metabolic rate is vital in reducing the risk of diabetes, heart disease and other obesity-related problems. Regular exercise is also vital for maintaining activity and increasing metabolic rate [9].

The aim of this study was to review feeding disorders and nutritional needs in patients with SCI. A review of the current literature was performed by using the online PUBMED database and the following keywords: "spinal cord injuries" AND ("diet" OR "nutrition" OR "malnutrition" OR "feeding" OR "eating disorders" OR "nutritional needs"). The search included studies that were written in English language and were published after 2000. Studies in other than English language, non-adult studies, experimental studies, review papers, commentary papers, and study protocols were excluded from this review

Discussion

The primary search retrieved a total of 509 papers. After screening of titles and abstracts, 426 articles were rejected as irrelevant with the topic. Of the remaining 83 publications evaluated, 43 were rejected for various reasons. After reviewing the reference lists of the remaining studies, 7 more studies were identified. Finally, 47 studies were included in the present review (Table 1).

Feeding disorders

Diet plays an important role in the rehabilitation of SCI patients. Patients with SCI often suffer from anorexia. Between the 2nd and 4th week after injury, weight loss becomes apparent [10]. In the acute phase, patients with cervical SCI may suffer from respiratory insufficiency due to neurologic impairment of respiratory muscles and autonomic changes that, occasionally leading to temporary or permanent artificial ventilation and disturbance of normal feeding. Dysphagia, following cervical SCI is an under-recognized complication leading to an increase of complications and morbidity. The term dysphagia is used to describe swallowing disorders, which affect the smooth transport of food from the oral cavity to the stomach. The incidence of dysphagia has been reported to be as high as 40% [11-12]. Dysphagia requires early diagnosis and special management to prevent possible complications. Risk factors include age, tracheostomy, ventilator use, nasogastric tube and anterior spinal surgery [7,11,13]. The latest has been associated with more than 50% risk of developing swallowing impairment and post-operative dysphagia [14-17]. Surgical implants in the anterior cervical spine may compress the pharynx or esophagus and change the pressures during swallowing. Moreover, anterior neck muscles supporting swallowing can be stretched or damaged intraoperatively. The recurrent laryngeal nerve, innervating most of the intrinsic neck muscles, may be damaged during anterior of cervical approach, causing dysphagia and hoarseness. The impairment of sensation disables patients from feeling the food or liquid residuals in the valleculae and pyriform sinuses [18]. Patients with dysphagia are at higher risk for pneumonia due to aspiration, atelectasis and prolonged hospitalization [12]. Aspiration is defined

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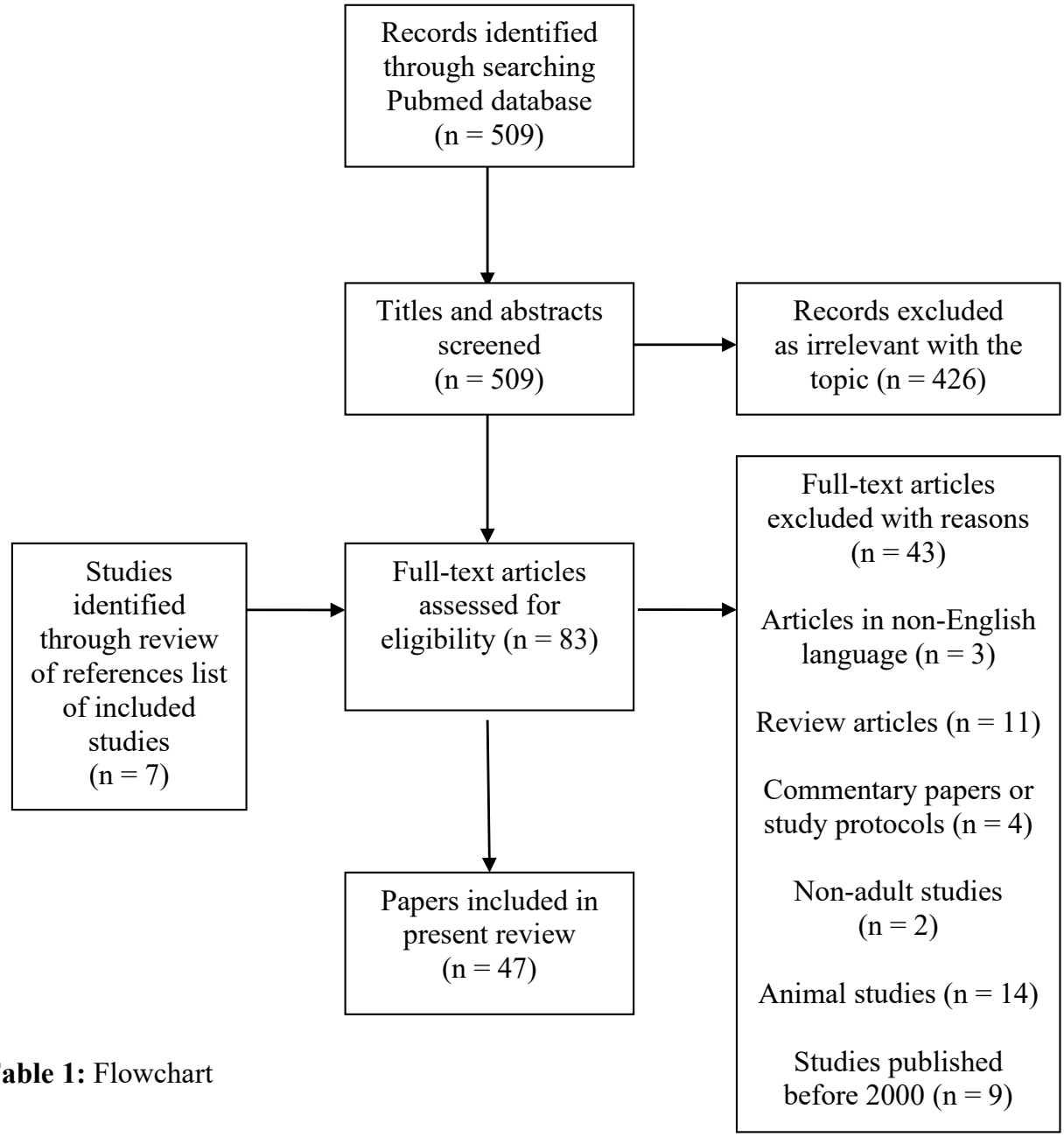

Table 1: Flowchart

as the passage of material (such as oral secretions, food or drink, or stomach contents) from the oropharynx or gastrointestinal tract into the larynx, below the vocal cords. Under normal conditions, in case of aspiration, coughing will clear the respiratory tract. However, in patients with high level SCI, this protective cough reflex is often disrupted [12,19]. The symptoms of dysphagia include coughing or choking, clearing of throat, watery eyes, runny nose, wet vocal quality during or after meals, decreased excursion of larynx or uncoordinated laryngeal movement, audible swallow, weight loss and unexplained, recurrent pulmonary infections.

Another complication of cervical and thoracic SCI, usually seen in the acute post-traumatic period, is ileus. The stomach becomes atonic and significantly stretched. For this reason, a nasogastric tube is placed to empty the stomach and to reduce the risk of aspiration.

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Aerophagia is also common in these patients. When ileus is restored, the nasogastric tube is replaced with a nasoduodenum tube to feed the patient while he is under mechanical ventilation or cervical traction. Stress gastric ulcer, with gastrointestinal bleeding, is another major complication, usually occurring on the 10th-14th post-traumatic day, mainly in quadriplegic patients taking steroids, with an incidence of more than 20%. Early administration of sucralfate and early intestinal feeding are required as a precaution.

Nutritional needs

The risk of under-nutrition and malnutrition in SCI patients is high [20-24]. Nutritional needs in SCI patients include: the need for energy production, the need for protein intake and the need for hydration. Particular attention should be paid to metabolic variations and the nutritional status of SCI patients, with a focus on improving their main medical problems [25].

Acute phase

In the immediate aftermath of injury, various hyper-metabolic and hyper-catabolic processes and responses have been documented, that may lead to malnutrition, loss of muscle mass, increased susceptibility to infection and reduced healing ability to pressure ulcers [26-28]. The paralysis and functional losses that usually occur after SCI produce additional metabolic and eating disorders. These eating disorders are more important in the acute phase, where they play a decisive role in patient's future course. During the first month after injury, decreased serum protein levels associated with malnutrition increase mortality in patients with cervical SCI [29]. Optimal nutritional evaluation and patient management can potentially minimize complications associated with acute injury and long-term rehabilitation [30]. The loss of muscle tone due to muscle paralysis below the site of injury results in decreased metabolic rate, initial weight loss and increased risk of osteoporosis [31]. In the acute post-traumatic period, the patient is likely to lose part of his body weight. To prevent excessive weight loss, acceptable body weight limits have been set. For patients with paraplegia and quadriplegia, these limits are 5% to 10% less than the ideal body weight and 10% to 15% less than the ideal body weight, respectively [32]. At the initial post-traumatic period, when patients cannot consume enough food orally, a more aggressive support should be chosen to ensure that they receive necessary amount of basic nutrients. Intestinal feeding initiated within 72 hours is an alternative method of intervention. A patient with a functioning gastrointestinal tract may be given intestinal support when he should not or cannot receive oral nutrition [33-34]. Patients with acute SCI tend to be malnourished at first due to traumatic stress, anorexia, and possible sepsis. As it is well known, effective resuscitation and release from mechanical ventilation also depends on good nutrition. Total parenteral feeding is early initiated after the injury and as soon as the digestive function is restored, it may be replaced by intestinal feeding. This type of nutritional support is indicated in patients who have gastrointestinal tract dysfunction and inability to swallow food (increased risk of aspiration) or greater tolerance to intestinal nutrition. As with intestinal nutrition, the duration of support influences the decision to prevail over one of the 2 available lines: peripheral parenteral nutrition and central or total parenteral nutrition. The peripheral parenteral nutrition is considered a short-term complementary intervention. It is recommended to use it for a period of less than 14 days, where it is used for transitional treatment [7].

Rehabilitation phase

In the rehabilitation phase, the nutritional needs of SCI patients are observed to decrease by 25% to 50%, due to the reduced mobility and the severe limitation of the muscle tone. This results in a significant increase in the likelihood of developing obesity and metabolic syndrome, which complicates the recovery process and compromises functional independence [31,35-39]. Patients with chronic SCI have a higher total body fat content in comparison with acute SCI patients [40]. On the other hand, physical disability may incommode feeding causing under-nourishment [41]. Finally, prolonged immobilization results in a reduction of patient's bone mass due to bone demineralization, thereby increasing the risk of osteopenia, osteoporosis, and fractures. It is worth noting that patients with quadriplegia should receive almost the same amounts of micronutrients and macronutrients as they would if they were not quadriplegic. Therefore, their food

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quantity does not change significantly, the only thing that changes is the way they eat their meals, since they are fed through intestinal catheters [42-43].

Western food pattern is mostly associated with increased serum triglycerides and cholesterol levels for SCI patients [44]. In contrast, fruits and vegetables are essential for adequate dietary intake of nutrients and a high-protein diet improves insulin sensitivity and bone mass [45-46]. SCI has been associated with a state of chronic low-grade inflammation. Anti-inflammatory diet has been found to reduce pain and edema and improve cognition and mobility [47]. In a randomized, controlled clinical trial, a 3-month anti-inflammatory diet was effective at reducing chronic inflammation in patients with SCI [48].

Neurogenic bowel and constipation are common in SCI patients, affecting their appetite. A healthy diet can help manage these symptoms. Fiber is a key aspect for bowel regulation. It is recommended to receive 30 gr of fiber per day to help the intestine component move through the bowel [49]. However, for some patients, having more than 20 gr of fiber per day can increase the chance of constipation. So, patients should gradually increase their fiber intake and evaluate the response. Good sources of fiber are whole grain breads, fruits and vegetables as well as whole grains such as popcorn. Consuming large amounts of water is also recommended to make the bowel component softer. It is recommended that SCI patients drink 1.5 liters of water a day [50]. Sometimes, increasing the fiber content of the diet and increasing fluid intake are usually not enough to treat the problem and laxatives are often required.

Another major problem for these patients is the increased likelihood of developing ulcers, which contribute to increased morbidity. Maintaining a good level of nutrition through a balanced diet and adhering to personal hygiene rules can help the prevention of bed sores [51]. To help the healing of ulcers, it is essential for SCI patients to receive enough proteins (more than 1.5 gr / kg / day) in their diet. The recommended caloric intake is 30 kcal / kg / day. Regular food intake is important to prevent skin breakdown while making sure that every meal contains a variety of nutrients, vitamins and minerals. Another crucial aspect of preventing skin ulcers is to drink plenty of water to ensure that skin is sufficiently hydrated [52].

People with SCI are also at increased risk for urinary tract infections (UTIs). It is important to drink plenty of water so that the urine is light in color. However, too much water can lower blood sodium causing confusion, cramps, and chills, so it is vital to ensure that there are sufficient minerals in the personalized diet of these patients. In general, SCI patients should drink water about half a liter more per day than the general population to prevent UTIs and to maintain proper bowel function [53]. Cranberry juice is also known to help prevent UTIs by reducing the levels of bacteria in the urinary tract. A glass of pure blueberry juice up to three times a day can help [54].

Dietary recommendations

Literature data are scarce concerning the best suitable diet for chronic SCI patients to lower cardiovascular risks. Given their lower metabolic demands, the evaluation of energy equilibrium is vital to define the appropriate caloric deficit for the prevention of cardiovascular disease. For this purpose, diets should decrease or exclude high-caloric foods, such as saturated fats, simple sugars, refined grains, and alcohol. In a prospective comparative study by Szlachcic et al, dietary intervention with reduced consumption of fat, sodium and alcohol was proven to be an effective initial treatment for 222 SCI patients, reporting positive alterations in lipid and metabolic profiles [55]. Recommended daily caloric intake is 1200 kcal; otherwise 23 kcal / kg / day for tetraplegic patients and 28 kcal / kg / day for paraplegic patients. Recommended protein intake is 0.8 mg / kg / day. A 6-month Mediterranean-style diet with a daily intake of 1200–2000 kcal along with resistance exercise led in reduction of body mass and sugar levels in obese SCI patients [4].

The use of nutritional supplements is common in SCI patients, especially in older adults and under-nourished patients [41, 56-57]. However, in a prospective cohort study, by Javierre et al, including 19 SCI patients, a daily supplementation of 1.5 gr of docosahexaenoic acid and 0.75 gr of eicosatetraenoic acid, was found to cause no significant changes in serum lipid levels [57]. Vitamin D supplementation is useful for maintaining normal plasma 25(OH)D levels

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[58-59]. In a prospective comparative study, 34 elite athletes with SCI received 35000 to 50000 IU of vitamin D per week, for 4 to 8 weeks. The authors observed that after supplementation, 91% of the participants had normal serum levels of vitamin D, when only 26% of the participants had normal serum levels of vitamin D before supplementation [59]. Similar were the results of a prospective, placebo-controlled trial by Flueck et al, assessing the supplementation of 6000 IU of vitamin D per day, in 20 elite wheelchair athletes with SCI. All athletes that received vitamin D increased serum levels to optimum [60]. In addition, it has been found that relatives should be involved in SCI patients' nutrition, as they appear to affect dietary behavior [61]. British NHS Guidelines recommend that SCI patients should receive 700 mg of calcium per day, vitamin D supplementation in ages over 65, five portions of fruit and vegetables per day, less than 70 gr of processed meat per day and less than 6 gr of salt per day [62]. Australian Dietary Guidelines recommend that chronic SCI patients should receive daily 2 portions of fruits, 5 to 7 portions of vegetables, 3 to 6 portions of grains foods, 2 to 3 portions of lean meat, 3 to 4 portions of milky products and 15 to 20 gr of fiber. Less than 30% of calories should be received by fat [63].

Conclusions

Patients with SCI are disabled for life and must change their lifestyle greatly. Injuries in cervical spine may compromise the process of swallowing, causing dysphagia and respiratory complications. In addition, the risk of under-nutrition and malnutrition in is high. Poor diet negatively affects overall health leading to obesity and causing cardiovascular disease, diabetes mellitus and metabolic syndrome. Patients with SCI must follow a proper diet to ensure that the right amount of nutrients is delivered for sustaining the appropriate physiological mechanisms.

Conflict of interest

The authors declare no conflicts of interest.

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Pharmacological approach for the management of chronic low back pain

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ABSTRACT

Chronic low back pain is a common condition affecting a high percentage of the general population. Affected people report diminished quality of life due to pain and disability. In terms of pharmacological treatment, physicians have a wide variety of options to choose from non-steroidal anti-inflammatory drugs (NSAIDS), opioids, non-opioids, muscle relaxants, antidepressants, antiepileptic drugs and biologic agents. However, there is no consensus as far as the optimal treatment is concerned.
A review of the current literature was performed to assess the efficacy and possible side effects of the different pharmacological treatments used in chronic low back pain and possibly give some guidelines about their use. The Pubmed and Cochrane databases were used to identify studies regarding the pharmacological treatment of chronic low back pain.

Key Words: chronic low back pain, medications, doses, effect

Introduction

Low back pain or lumbosacral pain refers to pain and discomfort, localized below the costal margin and above the inferior gluteal folds with or without leg pain [1]. Chronic low back pain (CLBP) lasts longer than 12 weeks. Non-specific low back pain includes symptoms that cannot be attributed to a known condition as infection, tumor, osteoporosis, ankylosing spondylitis, fracture, inflammatory process and cauda equina syndrome [2]. Pain is a multidimensional sensory experience that is unpleasant and may differ in intensity (mild, moderate, severe), quality (sharp, burning, dull), duration (transient, intermittent, persistent) and referral (superficial, deep, localized, diffuse). In addition, it has a strong emotional component. Pain is associated with avoidance, motor reflexes and alterations in autonomic output [3]. Low back pain is a common complaint among the general population with a subgroup of patients developing chronic and disabling symptoms generating large societal costs. In developed countries, about 70% of people develop low back pain at some time in their life, which usually improves at 2 weeks, but 10% of them are not able to work and 20% of them report sustainable symptoms for 1 year [4]. Low back pain occurred in 63.5% of workers at Kosovo energetic corporation [5]. Most primary care physicians can expect to see at least one patient with low back pain per week. The extended loss of function

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is also a financial burden for the social security systems since it results in loss of work productivity, treatment costs and disability payments [6]. It is estimated that the range of costs is about $ 12.2 to $ 90.6 billion, annually [7].

Generally, conditions causing CLBP can be categorized as: a) non-specific or idiopathic (70%): lumbar sprain or strain, b) mechanical (27%): degenerative process of disk, facets, fracture, spondylosis, c) referred pain (2%): diseases of pelvic organs, gastrointestinal disease, pancreatitis, d) non-mechanical (1%): neoplasia, multiple myeloma, spinal cord tumors, Paget disease of bone [6,8].

The main goal of physicians is to alleviate pain. Conservative treatment can be applied through several pharmacological factors, including acetaminophen, non- steroidal anti-inflammatory drugs (NSAIDS), opioids, non-opioids, muscle relaxants, antidepressants, antiepileptic drugs, biologic drugs and steroid epidural injections. However, there is no consensus as far as the optimal treatment is concerned. For this reason, a review of the current literature was performed to assess the efficacy and possible side-effects of the different pharmacological treatments applied in chronic low back pain and possibly provide guidelines on their use. The Pubmed and Cochrane databases were used to identify studies regarding the pharmacological CLBP treatment. The key words "chronic low back pain", "medications", "doses" and "effect'' were used.

Discussion

A wide variety of studies for CLBP were found (n= 1572). Most of them were excluded because of the different approach of treatment that was recommended (n= 1226). Remaining articles assessed for eligibility were 346. However, a great number of articles were also excluded for different reasons. Finally, 49 studies were included in the review (Table 1).

Acetaminophen

The first line of treatment of low back pain is usually acetaminophen (paracetamol). Paracetamol has been available for more than 100 years. In a recent study, the authors collected the clinical guidelines from different countries concerning the use of paracetamol in low back pain since 2016 [9]. In 2016, in Australia. paracetamol was initially prescribed for acute low back pain. In 2017, clinicians in Belgium did not recommend paracetamol as single pain medication, however on the same year in Canada acetaminophen was the first-choice medication for acute and chronic back pain, with NSAIDS being the second. Interestingly, on the same year both in the United Kingdom and United States, the use of acetaminophen was not recommended. However, in the Netherlands paracetamol may be prescribed as regularly as needed, while NSAIDS are not considered to be more effective than paracetamol [10,11]**.** Although many researchers express doubt about the efficacy of acetaminophen in individuals with chronic non-specific low back pain [9], others consider the drug as a first-line therapy, mainly due to its high safety profile [6]**.** There is high quality evidence that tramadol with or without paracetamol in comparison with placebo can decrease the pain coming from CLBP within 3 months [12]**.** Finally, the American College of Physicians recommends as first line option of medication for low back pain acetaminophen or non-steroidal anti-inflammatory drugs [13].

Non-steroidal anti-inflammatory drugs (NSAIDS)

Another medication that is usually recommended for CLBP is NSAIDS. These drugs block COX-enzymes and as a result inflammation is inhibited. European Guidelines suggest that NSAIDS can be used for a short period of time, as far as chronic non-specific low back pain is concerned [14]. In Japan, the outcomes of a study about the most prescribed medications in patients with CLBP and osteoarthritis showed that approximately 90% of the patients received NSAIDS and that the less prescribed drugs were weak opioids (10,7% patients with OA and 20,6% patients with low back pain). Japanese guidelines also recommend COX-2 inhibitors and acetaminophen for chronic low back pain [15]. Typical doses of NSAIDS are: aspirin (40-80mg/day), indomethacin (25mg 2-3 times/day), celecoxib (100mg 1-2 times/day), naproxen (250mg 4 times/day), diclofenac (50mg 3times/day) and piroxicam (20mg/day) [16]. In a recent study, patients with CLBP were separated in 2 groups. The first group was treated with 400mg ibuprofen and the other with placebo. Twenty minutes post-treatment, the group of patients treated with ibuprofen had an important re-

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duction of nitric oxide metabolites in their serum. In both groups, there was a significant analgesic effect compared to baseline [17]. In another 6-week study, a comparison of the analgesic effect and safety of celecoxib (200mg twice/day) and tramadol (50mg/ 4 times per day) in individuals with CLBP took place. The study was performed twice including initially 796 subjects and 802 subjects in the second study. In both studies the groups of celecoxib demonstrated greater pain relief and less adverse effects than the group of tramadol (study 1: celecoxib group 63.2% and tramadol group 49.9%, study 2: celecoxib group 64.1% and tramadol group 55,1%) [18]. In another study, the cost utility of the most common treatments for CLBP was investigated. The two most common treatments were electro-acupuncture (EA) and NSAIDS. The group of patients that were treated with EA had a mean age of 41 years and the group of patients treated with NSAIDS had a mean age of 38 years. For the study, clinicians used the EuroQol five-dimension questionnaire. Finally, they reported that NSAIDS had greater cost than electro-acupuncture (497.77$ ± 85,2$ versus 461,48$ ± 57,8 $) for the year 2016 [19]. In a study, investigating the effects of NSAIDS on CLBP, the authors concluded that six of their included randomized controlled trials showed that NSAIDS were superior in decreasing pain than placebo, but not effective as far as the disability was concerned. Another study comparing NSAIDS and home exercise showed that the group of patients that exercised regularly had better results in decreasing disability, but not in pain reduction [20]. Although, NSAIDS are usually prescribed for CLBP, there are reports that these agents cause serious side effects such as gastrointestinal bleeding and cardiovascular irritations and thus a short-term use is recommended [16].

Opioids

Another pharmacological agent that doctors oftenly prescribe, is opioids. For CLBP, oral or transdermal weak (tramadol, codeine, tilidin) or strong opioids (morphine, oxycodone, hydromorphine) can be administered [14]. It is generally believed that opioids should be considered as second- or third-line option in controlling CLBP and should only be administered for a short period of time [21]. There is high-quality evidence that sustained-release tramadol (200-300mg) is more effective than placebo in reducing CLBP at 12 weeks [22]. Another study showed that short-term treatment (<4 months) can improve pain levels but does improve function of individuals with CLBP [23]. However, six trials including 1887 patients comparing strong opioids (morphine, hydromorphine, oxycodone and tapentadol) with placebo, showed that opioids were more efficient than placebo in reducing pain and improving function in patients with CLBP [23]. Another high-quality study comparing tramadol with placebo in patients with CLBP, concluded that tramadol was more efficient in managing pain and disability and in reducing VAS pain scores [24]. The NICE (National Institute for Health and Care Excellence) recommends weak (e.g. codeine) and strong opioids use only for a short period of time. In addition, the American College of Physicians recommends tramadol, if NSAIDS are not effective enough for pain relief in CLBP [25]. However, there is no evidence that opioids improve the quality of life and it is underlined that doctors should prescribe them in low dosages (e.g. not more than 50-100mg morphine per day). Another study compared the effect of opioid and non-opioid medications (NSAIDS, acetaminophen) in 234 patients with CLBP, hip and knee osteoarthritis, focusing on pain-related function and pain intensity over 12 months. The authors announced that opioids were non-superior than non-opioid medications; moreover they caused more adverse effects than the other drugs [26]. Adverse effects as tolerance, hyperalgesia, allodynia, dependence, constipation, dizziness, sweating and sexual impotence in long term use are usual during opioid treatment [14,27]. The American Society of Interventional Pain Physicians recommends that clinicians should assess pain and improvement of function periodically, in case they have prescribed opioids. They suggest that methadone should be given only if other opioids have failed. It is also underlined that long-acting or high dose drugs should be prescribed for unmanageable pain and adverse effects such as constipation should be monitored [28]. In a study of 50 patients with CLBP treated with intravenous naloxone (8mg), morphine (0.08 mg/kg) and placebo, it was shown that morphine was superior in pain relief compared to the other drugs. The authors concluded that morphine provided acute relief of chronic back pain in patients with lower

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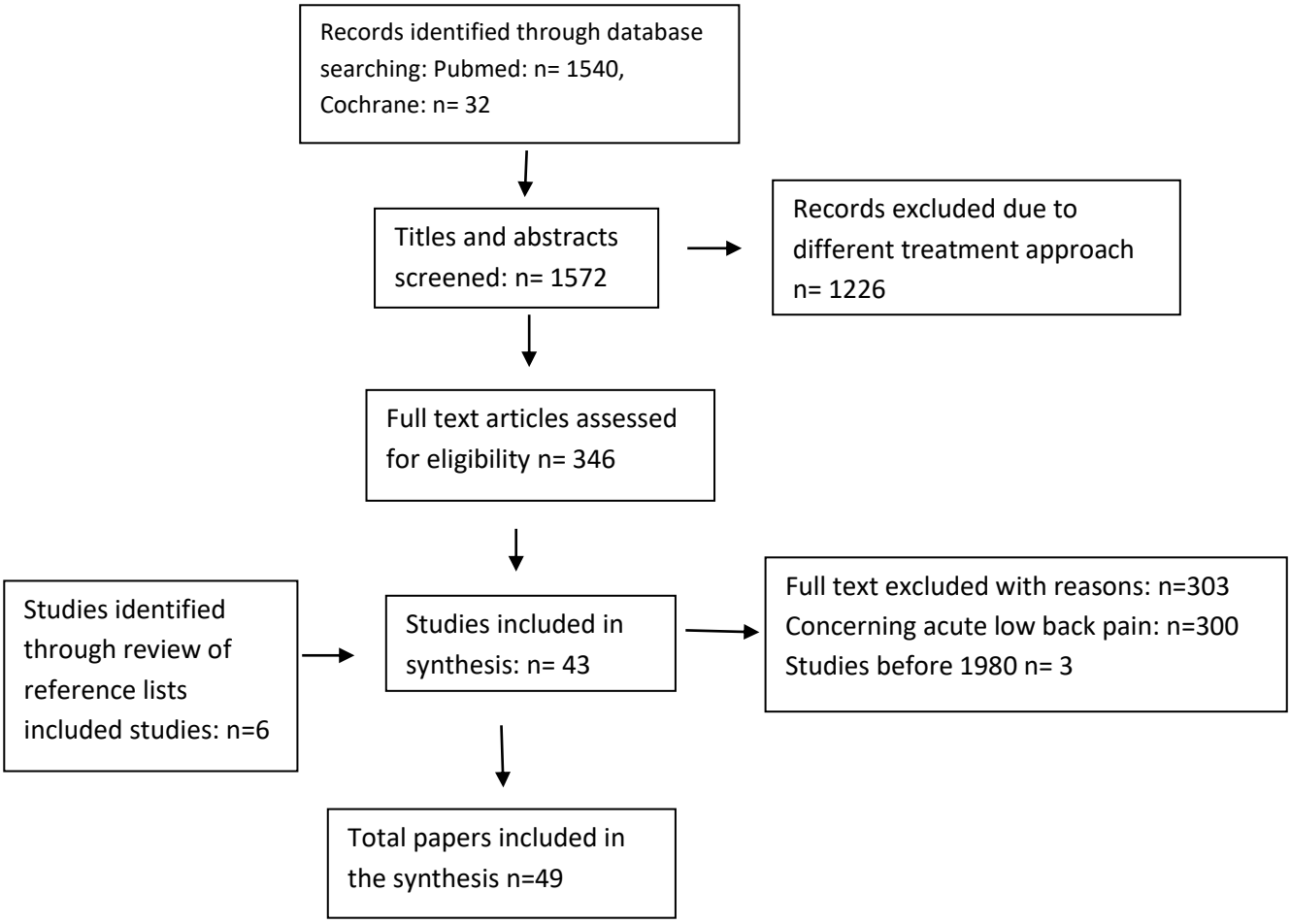

Table 1: Flowchart

natural opiodergic inhibition of chronic pain intensity [29]. Other clinicians investigated the effect of opioid treatment in Negative Affect (NA: distress, anxiety, depression) in a period of six months. Patient sample included 31 patients with chronic discogenic back pain with pain intensity >3/10 and was separated into 2 groups: a) high levels of Negative Affect b) low levels of Negative Affect. The authors concluded that hyperalgesia changes the pain inflection and affects patients' distress and that this process may not be beneficial to high NA patients [30].

Muscle Relaxants

These agents affect skeletal muscles by reducing muscle tone. Some examples of muscle relaxants are benzodiazepines, carisoprodol and dantrolene. It is generally believed that muscle relaxants are effective for a short-term use in the management of CLBP; however, their long-term use is not suggested due to adverse effects as dependency [31]. In a low-quality study, benzodiazepines (tetrazepam 50mg/3 times daily) were compared with placebo showing that benzodiazepines would be effective following treatment for 10-14 days. However, adverse central nervous system effects such as dizziness and drowsiness were reported [32]. European Guidelines suggest short-term use of muscle relaxants for controlling CLBP; however, they should be administered with caution because of multiple adverse effects such as addiction, allergies, reduction of liver function and gastrointestinal complications [14].

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Antidepressant and Antiepileptic drugs

Antidepressant and antiepileptic drugs are frequently prescribed for CLBP. The most common antidepressants used are tricyclic antidepressants. Antidepressants influence pain transmission in the spinal cord by inhibiting the reuptake of norepinephrine and serotonin [33]. Antiepileptic drugs, such as gabapentin, constitute an option for neuropathic pain. They act by enhancing the transformation of gamma-aminobutyric acid (GABA) to glutamate and by enhancing the ion channel action and/or the non-synaptic GABA release [14]. It is suggested that low doses of amitryptiline can be effective in reducing pain at 6 months and disability at 3 months in patients with CLBP [34]. In another study, tricyclic antidepressants relieved one in every 2 or 3 patients with peripheral neuropathic pain, serotonin noradrenalin reuptake inhibitors relieved one in every 4 or 5 patients and selective serotonin reuptake inhibitors relieved one in every 7 patients [35]**.** Fifty patients with non-specific CLBP took part in a study which examined the action of oral imipramine (75mg) in comparison to active placebo (1 mg of tolterodine). It was found that imipramine was not effective in CLBP [36]. In another study, antidepressants were compared with placebo in 504 participants having CLBP. Antidepressant treatment reduced pain level in contrast with the placebo, but it was not efficient enough to improve patients' daily life. About 22% of patients treated with antidepressants faced adverse effects. [37]. There is another mention that noradrenergic-serotoninergic antidepressants can alleviate pain in patients with CLBP [37, 38]. Although there is strong evidence for the action of antidepressants, it is reported that 20% of patients receiving these agents have an adverse reaction such as drowsiness, dry mouth, dizziness and constipation [37]. Another 8-week study which included 74 patients with CLBP compared the effect of 150mg maprotiline (norepinephrine reuptake blocker) with that of 30mg paroxetine (serotonin reuptake blocker) and that of 37.5mg active placebo (diphenhydramine hydrochloride). Pain intensity reduced 45% with maprotiline, 27% with placebo and 26% with paroxetine. In conclusion, noradrenergic agents were found to be superior to selective serotoninergic reuptake inhibitors [39]. Strong evidence supports that tricyclic antidepressants assist in conditions like neuropathic pain, low back pain and fibromyalgia [40]. Another study compared pregabalin (antiepileptic, usually prescribed in neuropathic pain) and celecoxib (selective syclo-oxygenase-2 inhibitor) in 34 patients with CLBP. The authors concluded that the combination of pregabalin and celecoxib showed better results in reducing CLBP, according to the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS score) [41]. In another high-quality study the authors reported that anticonvulsants (gabapentin, pregabalin) are able to help patients handle their CLBP, but the risk of adverse effects is high [42]. However, there is a study which causes second thoughts about the action of pregabalin. In this study, 44 patients with CLBP received pregabalin (35mg/hr) for 3 weeks and then they were randomized in two groups. The first group received 35mg/h transdermal buprenorphine plus 300mg/day pregabalin and the second group received 35mg/h transdermal buprenorphine plus placebo. The results were that the group which received pregabalin with transdermal buprenorphine had significant pain relief and had better quality of sleep [43].

Epidural injections-Cortisone-Biologic Agents

Epidural injections sometimes are used for the management of CLBP. A recent study concluded that epidural injections with steroids or local anesthetic helped patients to reduce CLBP by ≥50% and improve their function by 60% according to the Oswestry Disability Index [44]**.** However, another study reported that epidural steroid injections should not be in the first line of treatment due to the side effects that may produce, despite the short-term relief of pain and early return to daily life [45]. In a recent study, epidural injections of cortisone were found to be helpful in 82% of patients with acute discogenic pain, but when administered in patients with unstable spine or previous laminectomy (having pain for over 3 months), they were found ineffective [46]. Other researchers tested cortisone injections in combination with other therapies such as manipulation, mobilization, muscle stretching and traction in patients being in the acute and sub-acute phase of low back pain. Patients were randomized in two groups. The first group was treated with conventional therapy by primary health clinicians and the second group was treated with ma-

nipulation, stretching, mobilization and cortisone injections. The group treated with manipulations and cortisone injections had better results than the group with conventional treatment [47]. Finally, according to the American College of Physicians, systematic corticosteroids do not seem to be effective for the management of low back pain [48].

The last option in the management of CLBP is biologic agents as the anti-tumor necrosis factor-alpha (Anti-TNF-a) and the anti-nerve growth factor (anti-NGF). It has been reported that Anti-TNF-a is able to reduce pain and enhance function but there is no evidence that it is superior to placebo. On the other hand, Anti-TNF-a use has been shown to reduce the number of invasive procedures such as discectomy and radicular block in case of sciatica. Additionally, anti-NFG can alleviate pain intensity and improve function when compared to placebo, although the risk of side effects is high [49]. However, there is need of further research upon anticytokine treatments and how they affect CLBP.

Conclusion

CLBP is a common condition affecting a high percentage of the general population. Affected people report diminished quality of life due to pain and disability. Physicians should choose the right drug in the right dose for each individual patient and always concern about the potential side effects. Further research is needed for promising new drugs to assess their efficacy and safety.

Conflict of interest

The authors declare no conflicts of interest.

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Management of post-operative pain in children and adolescents with scoliosis

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ABSTRACT

Post-operative pain management in children and adolescents undergoing scoliosis surgery remains a major concern. The aim of this study was to review the methods of post-operative pain management in such patients. For this reason, a review of the current literature was performed using the online PUBMED. Inclusion criteria in the review were: prospective, randomized, double-blind studies assessing methods of management of postoperative pain in children and adolescents subjected to spinal surgery due to scoliosis. Twenty-three prospective, randomized, controlled trials were finally included in the review. While intravenous patient-controlled analgesia with morphine remains the gold standard and most widely used analgesia technique for spinal fusion surgery in children and adolescents with scoliosis, other useful methods including epidural analgesia and intrathecal opioids as well as the administration of gabapentin, dexamethasone, acetaminophen and ketorolac seem to have beneficial effects. Taking into consideration the complexity of pain and the high rate of opioid-related adverse events, it is essential to establish a multimodal approach to improve postoperative analgesia.

Key Words: postoperative pain, analgesia, children, adolescents, scoliosis

Introduction

Scoliosis is defined as a three-dimensional structural deformity of the spine and its diagnosis is based on the measurement of the major spinal curvatures involved in the deformity. This measurement is traditionally performed using the Cobb method. An angle greater than 10° defines scoliosis.

There are several types of scoliosis such as idiopathic, functional, neuromuscular and degenerative [1]. Idiopathic adolescent scoliosis is the most common type (80%). It begins in early adolescence, has an incidence of 1-4% and usually affects young girls at the age of 10. Patients who are more skeletally immature are at greater risk of increasing deformities. For patients with a Cobb angle less than 20° careful follow-up is appropriate, while the use of braces is indicated in patients with Cobb angles exceeding 20°. Surgery is reserved for patients with idiopathic adolescent scoliosis who are believed to be at great risk of increasing curvatures during adulthood (Cobb > 40-45°). The primary goals of surgery are to reduce deformity and restore spinal alignment. Spinal fusion aims to prevent long-term

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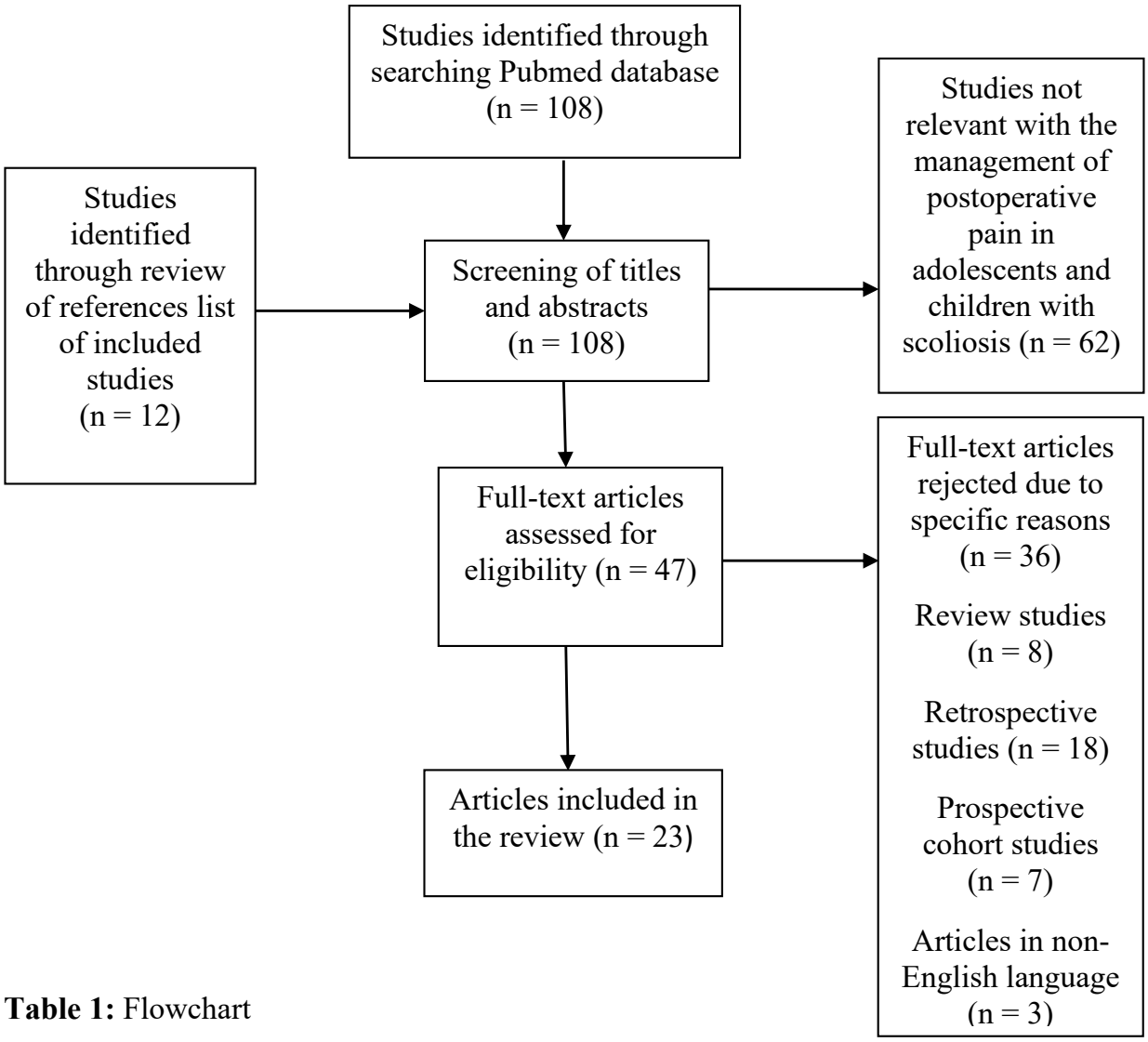

Table 1: Flowchart

consequences of large deformities, which may produce pain and impaired respiratory function [2].

The extensive dissection of bones and soft tissues that takes place during spinal surgery usually results in severe post-operative pain [3], the management of which can be very challenging. Under-treatment of post-operative pain usually reduces patient overall satisfaction and delays post-operative recovery and rehabilitation [4-5]. Intravenous (IV) patient-controlled analgesia (PCA) with opioids is the gold standard of postoperative pain management following spinal fusion. However, opioids have important side effects. Multimodal analgesia after scoliosis surgery has been recently introduced but there are contradictory results or inadequate data regarding its use.

The aim of this study was to review the methods of post-operative pain management in children and adolescents undergoing surgical correction of scoliosis.

Discussion

A review of the current literature was performed using the online PUBMED database and the following keywords: ("treatment" OR "management") AND ("post-operative pain" OR "analgesia") AND ("children" OR "adolescents") AND "scoliosis". Inclusion criteria in the review were: prospective, randomized,

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double-blind studies assessing methods of management of post-operative pain in children and adolescents subjected to spinal surgery due to scoliosis. Retrospective studies, cohort studies, reviews and studies in other-than-English language were excluded. The search resulted in 108 studies. After checking titles and summaries, 62 articles were rejected as irrelevant to the subject. Of the 47 remaining publications, 36 were rejected due to specific reasons. After reviewing the reference lists of the included studies, 12 more studies were included. Finally, there were 23 studies included in the review (Table 1).

Patient-controlled analgesia

PCA enables patients to intermittently regulate the administration of analgesics, mainly opioids, according to pain level. Although IV PCA is mainly used in adults with moderate to severe post-operative pain, it is also considered a safe and effective method of analgesia in children and adolescents [6]. Indeed, IV PCA using morphine is the most widely used method of postoperative analgesia in children and adolescents undergoing posterior spinal fusion for scoliosis [7-8]. The use of morphine is generally considered safe in children [9], as it carries a lower risk of respiratory depression than in adults [10-11].

The main complications of morphine-based IV PCA are nausea, vomiting and pruritus [12]. Several randomized controlled trials have examined the use of morphine in post-operative analgesia in children following spinal surgery for scoliosis [13-19]. Cassady et al, conducted a prospective, randomized study comparing the effectiveness of continuous thoracic epidural analgesia using bupivacaine and fentanyl with that of IV PCA using morphine, in the management of post-operative pain following posterior spinal fusion for idiopathic adolescent scoliosis. No significant differences were observed between groups in post-operative pain scores [13]. Another prospective, randomized study by Gauger et al, compared the effectiveness of patient-controlled epidural analgesia (PCEA) using hydromorphone and bupivacaine with that of IV PCA using hydromorphone, in managing postoperative pain in 38 children and adolescents undergoing posterior spinal fusion for scoliosis. Epidural catheters were found to provide modestly improved analgesia compared to IV PCA ($p \leq 0.042$) [14]. In a randomized prospective trial by Klatt et al, IV PCA, single and dual continuous epidural analgesia were compared in terms of post-operative pain reduction in 66 patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion. The authors concluded that double continuous epidural analgesia with two catheters provided stronger post-operative analgesia compared to single continuous epidural analgesia and IV PCA [15]. Another randomized double-blind, placebo-controlled trial by Munro et al, evaluated the analgesic effect of the combination of IV morphine-based PCA and IV ketorolac in 35 patients after posterior spinal fusion for scoliosis. The intervention group received 0.5 mg/kg of ketorolac along with IV PCA with morphine every 6 hours postoperatively and for 36 hours, while the control group received placebo. The combination of ketorolac and PCA with morphine was associated with reduced postoperative pain scores and opioids consumption [16]. Similarly, another randomized double-blind, placebo-controlled trial by Rusy et al, evaluated the analgesic effect of the combination of IV morphine-based PCA and oral gabapentin in 59 patients following posterior spinal fusion for scoliosis. The intervention group received IV PCA with morphine along with 5 mg/kg of gabapentin 3 times per day for 5 days, while the control group received placebo. The combination of gabapentin and PCA with morphine, was associated with reduced post-operative pain scores and opioids consumption [17]. Weldon et al, in a double-blind, prospective, randomized study, compared the analgesic effect of an intermittent PCA bolus versus PCA plus a continuous infusion (CI), in 44 children and adolescents undergoing elective scoliosis surgery. There were no differences between the PCA and PCA plus CI groups regarding post-operative pain relief and morphine consumption [18]. O' Hara et al, conducted another prospective, double-blinded, randomized study involving 31 patients subjected to elective posterior spinal fusion surgery for adolescent idiopathic scoliosis. Participants were randomized into 3 groups according to the epidural solution infused: Group A received 0.1% of bupivacaine and 5 mg/ml of fentanyl, group B received 0.0625% of bupivacaine and 5 mg/ml of fentanyl and group C received placebo. Intraoperatively, all patients received

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a midthoracic epidural catheter with a set infusion rate followed by IV PCA with morphine postoperatively. The authors concluded that epidural analgesia with bupivacaine and fentanyl had no superior analgesic effect over morphine-based IV PCA [19].

Epidural analgesia

The use of epidural analgesia as an adjuvant to IV PCA for post-operative analgesia in adolescents and children undergoing spinal fusion for scoliosis has been investigated in several randomized controlled trials [13-15,19-22]. Interestingly, the timing of the epidural catheter placement, the numbers and positions of the catheters inserted, the types and doses of drugs administered, and the mode of administration vary widely in the literature. However, the combination of epidural analgesia with IV PCA is more effective in pain reduction in comparison with IV PCA alone, reducing the post-operative quantity of analgesics [12,23]. The success and safety of this method may depend on appropriate techniques used. Reported complications include respiratory depression, neurologic changes, hypotension and over-sedation [24]. In a randomized prospective trial by Blumenthal et al, double continuous epidural analgesia and continuous IV morphine infusion were compared in terms of post-operative pain reduction. Thirty patients with adolescent idiopathic scoliosis were randomized to receive double epidural analgesia with ropivacaine 0.3% or continuous IV morphine infusion. Authors found that double continuous epidural analgesia with two catheters provided stronger post-operative analgesia compared to continuous IV morphine infusion. However, both methods provided efficient post-operative analgesia [20]. Another prospective, randomized, double-blind study by Erdogan et al, compared the effectiveness of patient-controlled intermittent bolus epidural analgesia with that of patient-controlled continuous epidural analgesia, in managing post-operative pain in 47 children and adolescents undergoing posterior spinal fusion for scoliosis. There were no differences in pain scores between the groups. However, post-operative opioid consumption was lower in the patient-controlled intermittent bolus epidural analgesia group [21]. Cohen et al, conducted a prospective, randomized study comparing the effectiveness of extended-release epidural morphine (150 μg/kg) with that of intrathecal administration of morphine (75 μg/kg) in managing postoperative pain in 71 patients undergoing elective scoliosis surgery. No significant differences were observed between groups in post-operative pain scores and total morphine consumption [22].

Intrathecal administration of opioids

As it has been reported in several randomized controlled trials, intrathecal administration of opioids, mainly morphine, after intubation and prior to surgical incision, may reduce post-operative pain and opioid consumption [22,25-27]. However, the duration of this analgesic effect is less than 24 hours. Therefore, this method should be combined with IV PCA. The complications of intrathecal opioid administration are the same as those of IV PCA [28]. In a randomized, prospective trial by Goodarzi et al, intrathecal administration of morphine and sufentanil and IV morphine infusion were compared in terms of post-operative pain reduction, in 80 patients with adolescent idiopathic scoliosis. The authors concluded that intrathecal administration of morphine and sufentanil provided prolonged post-operative analgesia compared to IV morphine administration [27]. The appropriate intrathecal dose of morphine was evaluated in another prospective, randomized trial by Eschertzhuber et al. Forty-six children undergoing scoliosis surgery were randomly allocated to receive 5 μg/kg of morphine plus 1 μg/kg of sufentanil, 15 μg/kg of morphine plus 1 μg/kg of sufentanil intrathecally, or placebo. Both doses of intrathecal morphine succeeded in producing sufficient post-operative analgesia and lower opioids consumption in comparison to placebo [25]. Similarly, Gali et al, evaluated the optimal dose of intrathecal morphine in a prospective, randomized trial. Thirty children undergoing scoliosis surgery were randomly allocated to receive 5 μg/kg of morphine, 2 g/kg of morphine intrathecally, or placebo. Postoperatively, all patients received IV PCA with morphine. The authors concluded that both doses of 2 and 5 μg/kg intrathecal morphine along with IV PCA with morphine, had a stronger analgesic effect in comparison to IV PCA with morphine alone after spinal fusion in children [26].

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Ketamine

Ketamine, an N-methyl-D-aspartate receptor antagonist, is occasionally used to treat neuropathic pain. Four randomized controlled trials have investigated the effects of continuous ketamine infusion in post-operative pain reduction in children and adolescents subjected to spinal surgery due to scoliosis, with controversial results [29-32]. In a prospective, randomized, double-blind, placebo-controlled trial by Perello et al, the analgesic effect of IV administration of ketamine was evaluated in 44 pediatric patients subjected to scoliosis surgery. The intervention group (n=21) received a bolus IV dose of 0.5 mg/kg of ketamine followed by a continuous IV infusion of 2 μg/kg/min for 72 hours postoperatively, while the control group received placebo (n=23). The authors found no statistical difference in post-operative opioids consumption in patients receiving ketamine [31]. Similar were the results of another double-blind, prospective, controlled trial by Pestieau et al. Fifty patients undergoing posterior spinal fusion for scoliosis were randomized to receive peri-operative low-dose ketamine or placebo. The intervention group received a bolus dose of 0.5 mg/kg preoperatively, an intraoperative infusion of 0.25 mg/kg/hr followed by continuous IV infusion of 0.1 mg/kg/hr. The authors found no statistical differences in post-operative pain scores and opioids consumption in patients receiving ketamine [32]. Another prospective, randomized, controlled trial by Engelhardt et al, evaluated the analgesic effect of ketamine in 34 children undergoing scoliosis surgery. Intervention group received a bolus dose of 0.5 mg/kg of ketamine followed by a continuous infusion of 4 mg/kg/min, while placebo group received an equal volume of saline. Post-operative morphine consumption and pain scores did not differ significantly between groups [29]. Minoshima et al, conducted a prospective, randomized, controlled study assessing the effectiveness of combined intra-operative and post-operative administration of ketamine in managing the post-operative pain in 36 patients undergoing posterior scoliosis surgery. The intervention group had intra-operative and post-operative administration of ketamine at a rate of 2 μg/kg/min until 48 hours post-operatively. The control group received equal volumes of saline. The authors observed that post-operative opioids consumption was lower in the ketamine group. Pain scores were similar in both intervention and control groups [30].

Gabapentin - Pregabalin

Anticonvulsant agents, such as gabapentin, have been widely used for the management of chronic neuropathic pain. In scoliosis surgery, two randomized controlled trials have evaluated the analgesic effect of gabapentin in postoperative pain, with contradictory results [17,33]. In a prospective, randomized, double-blind, placebo-controlled trial by Mayell et al, the analgesic effect of IV administration of gabapentin was evaluated in 36 patients subjected to scoliosis surgery. The intervention group (n=18) received a single pre-operative dose of 600 mg of gabapentin, while the control group received placebo (n=18). The authors found no statistical difference in post-operative opioids consumption in patients receiving gabapentin [33]. Another randomized, double-blind, placebo-controlled trial by Rusy et al, evaluated the analgesic effect of the combination of IV morphine-based PCA and oral gabapentin in 59 patients after posterior spinal fusion for scoliosis. The intervention group received IV PCA with morphine along with 5 mg/kg of gabapentin 3 times per day for 5 days, while the control group received placebo. The combination of gabapentin and PCA with morphine was associated with reduced postoperative pain scores and opioids consumption [17]. Recently, gabapentin was reported to have significantly beneficial analgesic effect when administered as a part of a multimodal pain management protocol (ketorolac, acetaminophen, hydromorphone and oxycodone), particularly in the first 48 hours after surgery [34]. In a recent prospective, randomized, placebo-controlled study, the authors found that another anticonvulsant, pregabalin, does not affect post-operative pain scores and opioid consumption after scoliosis surgery in adolescents [35].

Acetaminophen - NSAIDs

Administration of acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) decreases post-operative pain and opioid consumption. Two randomized, controlled studies have evaluated the analgesic effect of acetaminophen in patients undergoing spinal fusion

for scoliosis, showing beneficial effects in post-operative analgesia [12, 36]. In a prospective, randomized, double-blind, placebo-controlled trial by Hiller et al, the analgesic effect of IV administration of acetaminophen was evaluated in 36 patients subjected to scoliosis surgery. The intervention group received IV 30 mg/kg of acetaminophen at the end of surgery and thereafter twice at 8-hour intervals. The authors concluded that acetaminophen provided post-operative pain reduction but did not affect opioids consumption in the first 24 hours [12]. Another prospective, randomized study by Olbrecht et al, recruited 114 patients undergoing spinal fusion for adolescent idiopathic scoliosis. The intervention group (n=44) received IV acetaminophen while the control group received placebo. All patients received IV PCA post-operatively, along with ketorolac and diazepam. The authors found a negative association between IV acetaminophen administration and post-operative opioids consumption [36]. The combination of ketorolac and PCA with morphine, was associated with reduced post-operative visual analogue scale (VAS) scores and opioid consumption, in another randomized, double-blind, placebo-controlled trial by Munro et al, where 35 adolescents were randomly assigned to receive placebo or 0.5 mg/kg of ketorolac along with IV PCA with morphine every 6 hours post-operatively for 36 hours [16]. However, there is a concern about post-operative bleeding and the potentially harmful effects of NSAIDs on bone healing, a vital process for successful spinal fusion [37-38].

Steroids

Steroids have been widely used in adults for the management of postoperative pain. A recent randomized controlled trial has shown that post-operative administration of dexamethasone after posterior spinal fusion was associated with a 40% decrease in post-operative use of opioids, with no increase in wound complications [39].

In conclusion, IV PCA with morphine remains the gold-standard and most widely used method of analgesia in children and adolescents with scoliosis undergoing spinal fusion. Other useful methods include epidural analgesia, intrathecal opioids and administration of gabapentin, dexamethasone, acetaminophen, and ketorolac. Taking into consideration the complexity of pain and the high rate of adverse events associated with opioids, it is essential to establish a multimodal approach to improve post-operative analgesia in children and adolescents subjected to spinal surgery due to scoliosis. A

Conflict of interest

The authors declare no conflicts of interest.

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Regional anesthesia techniques in patients with chronic spinal cord injury

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ABSTRACT

Anesthesia-related complications, such as autonomic dysreflexia, remain an issue in patients with spinal cord injury (SCI). The use of regional anesthesia is an alternative method for the prevention of autonomic dysreflexia that may occur during surgery in SCI patients. In addition, regional anesthesia has been used against neuropathic pain and spasticity. The aim of this study was to investigate the different applications of regional anesthesia in SCI patients. A review of the current literature was performed using the online PUBMED database and using the keywords "regional anesthesia" and "spinal cord injuries". Initial search results included 183 studies. Finally, 28 studies were included in this review. The results of this study showed that regional anesthesia may be particularly useful for patients with SCI. It may be used for upper and lower limb surgery, abdominal surgery, and obstetrics and particularly for the prevention of autonomic dysreflexia. Moreover, it may be used in the management of chronic neuropathic pain and spasticity in SCI patients. However, more high-quality studies are needed to clarify the benefits of regional anesthesia in the management and rehabilitation of SCI patients.

Key Words: regional anesthesia, spinal cord injuries

The human spinal cord, despite its unique cell architecture and its ability to rapidly transmit specialized information to the brain, is inherently deprived of the ability to regenerate, an ability which would allow it to restore the sequelae of an injury. Thus, the consequences of suffering a small-sized traumatic spinal cord injury (SCI) can be severe for the patient, with little chance of complete recovery of neurological function. The pathophysiological changes concern not only the injured spinal cord tissue, but also many important organs and systems of the body [1,2].

Patients with SCI may experience respiratory, cardiovascular, urological, gastrointestinal, musculoskeletal, and metabolic complications. Theoretically, in SCI patients any lower limb and abdominal surgery and delivery may be performed without anesthesia if there is no sensation at the operative site. However, especially with spinal lesions above the mid-thoracic region, autonomic dysreflexia may be provoked by situations like skin trauma and dilation or stimulation of the bladder, the intestine, the uterus, and the perineum [3]. Autonomic dysreflexia is a known emergency in SCI

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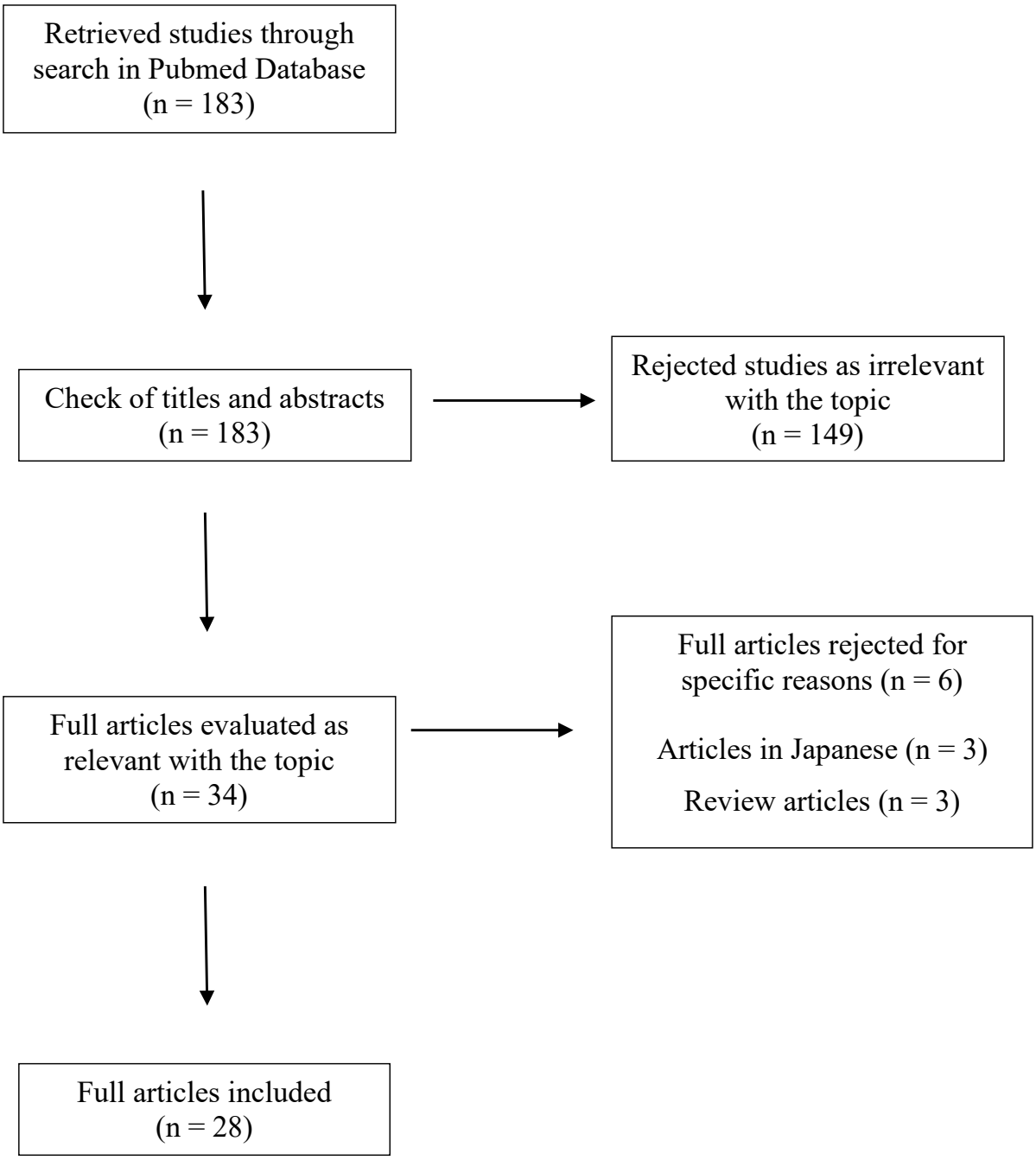

Table 1: Flowchart

patients. It is characterized by an acute rise in blood pressure and bradycardia, although tachycardia may also occur. It can present with a variety of symptoms and can vary in intensity, from asymptomatic to mild discomfort and headache to a life-threatening condition with blood pressure rising to 300 mmHg [4]. Autonomic dysreflexia is caused by spinal reflexes which remain intact, despite the patient's injury. A stimulus below the spinal lesion produces a centripetal impulse, which generates a sympathetic response, which in turn

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produces vasoconstriction below the neurological lesion [5]. The result is peripheral and visceral vasoconstriction followed by the development of hypertension. Untreated episodes can have serious consequences including intracranial hemorrhage, retinal detachment, seizures, and even death. It has been observed that the higher the level and the severity of SCI, the greater the degree of intensity of autonomic dysreflexia [4]. Stimulation of the lower urinary system is responsible for most episodes of autonomic dysreflexia, with bladder dilation being responsible for 75% to 85% of cases. Bladder dilation and stretching may result from blockage of bladder catheter flow or insufficient frequency of intermittent catheterization. The second most common cause of autonomic dysreflexia is the dilatation of the intestine that is responsible for 13% to 19% of cases. Diseases of the gastrointestinal tract, pressure ulcers, ectopic ossification and menstruation constitute other causes of autonomic dysreflexia [4].

The use of regional anesthesia is an alternative method for the prevention of autonomic dysreflexia occurring during surgery in SCI patients but has also been used against neuropathic pain and spasticity. The aim of this review was to investigate the different applications of regional anesthesia in SCI patients.

A review of the current literature was performed using the online PUBMED database and by using the key words "regional anesthesia" and "spinal cord injuries". Primary search results included 183 papers. After reviewing titles and abstracts, 149 studies were rejected as irrelevant. Of the remaining 34 studies evaluated, 6 were rejected. Eventually, 28 studies were included in this review [6-32] (Table 1).

Discussion

Advantages of regional anesthesia

Spinal anesthesia has been recommended for SCI patients, particularly for urological and obstetrical surgery. Its advantages are the reliable prevention of autonomic dysreflexia and the avoidance of certain hazards of general anesthesia. In a recent study including twenty-five SCI patients with lesions above T7 who underwent endoscopic urologic procedures, spinal anesthesia was found to be 100% successful in preventing autonomic dysreflexia, without being associated with hypotension [8]. In another study, spinal anesthesia with the use of hyperbaric cinchocaine was noticed to minimize the autonomic hyper-reflexic cardiovascular responses to bladder dilation and had minimal effects on cardiovascular measurements [7]. Another randomized, double-blind, placebo-controlled trial in twenty-six SCI patients with lesions above T6, showed that lidocaine anal intersphincteric block significantly reduces the autonomic dysreflexia response in SCI patients subjected to hemorrhoids ligation [10]. In addition, the topical induction of lidocaine gel immediately before rectal manipulation has been shown to minimize the rate and severity of autonomic dysreflexia in patients with cervical SCI [12].

Disadvantages of regional anesthesia

Previous spinal surgery, spinal contractures, spasticity and bony deformities may cause technical difficulties in the performance of neuraxial anesthesia and the identification of the desired sensory level [6,14]. Occasionally, the level of the nervous block can be identified by locating the level at which spastic paraparesis becomes flaccid. A case series study, suggested that the disappearance of Babinski sign and patellar tendon reflex along with the loss of spasticity may confirm the effect of spinal anesthesia in patients with cervical SCI, even though identification of the level of the block can be difficult [22].

In comparison to spinal anesthesia, epidural anesthesia has been reported to produce less satisfactory results. A few failures of prevention of autonomic dysreflexia have been reported, maybe due to distortion of the epidural space, wrong catheter position or imprecise evaluation of the effect of a test dose [14,20]. Maintenance of hemodynamic stability may not be sustained with isolated neuraxial administration of opioids. Epidural opioids such as pethidine and fentanyl, have been reported to hamper autonomic dysreflexia with conflicting results, as shown in published case reports [26-27].

Regional anesthesia for obstetrics

Spinal cord injury patients with lesions below T10 may experience pain during labor and patients with lesions between T5 and T10 may at least experience contractions. Regional anesthesia has been widely used in SCI obstetric patients [9,11,13,20-21, 28,30]. Regional

anesthesia may be more difficult to perform and have a higher failure rate in SCI patients, especially in the presence of surgical hardware and due to spasticity, deformities and difficulties with patient positioning [21]. In a case series by Sharpe et al, including 9 women with SCI, 67% had cesarean delivery [21]. Moreover, autonomic dysreflexia may be triggered by uterine contractions [26]. The prevention and control of autonomic dysreflexia during labor is based on the use of antihypertensive agents (nifedipine, hydralazine and verapamil) but the most used measure is epidural anesthesia. Epidural anesthesia may block autonomic dysreflexia during labor and after it, although its success may be variable [11,20]. Among 2 parturients with SCI, epidural block succeeded a full prophylaxis for autonomic dysreflexia [11]. Another study reported a case of a laboring SCI patient who developed autonomic dysreflexia and was successfully treated with epidural anesthesia [20]. The combination of spinal and epidural anesthesia or continuous infusion should be preferred over a single injection. The sufficiency of the anesthesia can be checked by blood pressure control [11]. The epidural catheter should be left in situ as autonomic dysreflexia may occur up to 48 hours after delivery [14].

Regional anesthesia for upper limb surgery

In case of upper limb surgery, brachial plexus block is a useful method of regional anesthesia. The axillary brachial plexus blockade is preferred over the supraclavicular block, due to decreased risk of pneumothorax. Bilateral brachial plexus block (right infraclavicular and left axillary block) has been successfully used in a SCI patient with a C5 lesion, for bilateral elbow fracture, without any respiratory complications [15].

Regional anesthesia for neuropathic pain

Chronic neuropathic pain is a serious complication of SCI, and regional anesthesia may have a role in its management. In a recent study, intrathecal administration of a combination of morphine and clonidine led to a 63% reduction of neuropathic pain in SCI patients [32]. In another study, neuraxial administration of 5% lidocaine was associated with a 37% reduction of neuropathic pain in 62% of SCI patients [17]. In a study by Glynn et al, epidural injection of morphine (5 mg) and/or clonidine (150 mg) in 15 SCI patients led to pain decrease in five patients [33]. In a similar study including 6 SCI patients, a single epidural administration of 150 mg of clonidine reduced more than 50% the neuropathic pain in 3 patients and improved muscle spasticity [29]. However, in another study, the intrathecal administration of baclofen in 9 SCI patients had no serious effect on reducing chronic pain [31].

Regional anesthesia for spasticity

Spasticity is one of the most common and potentially disabling complications affecting patients with SCI. Injection techniques are useful for treating local spasticity and improving functional outcome, with minimal adverse effects. Diagnostic blockades, usually performed with the use of lidocaine, may identify the muscles that are responsible for the spasticity, the differences between spasticity and contracture, and predict the contribution of a therapeutic block to functional improvement. When a spastic muscle is identified, therapeutic peripheral nerve blockades can be performed. Usually, the peripheral nerves subjected to chemical neurolysis have mainly motor distribution, such as the obturator and the musculocutaneous nerve. These blocks may relieve painful contractures and spasms and thus prevent bed sores, improve gait and facilitate nursing care, hygiene and positioning [25,34]. Alcohol or phenol is used for therapeutic nerve blocks, the effect of which lasts usually for 8 to 12 months [35]. Phenol acts on the nerve sheath causing serious nerve injury and eventually muscle atrophy. Alcohol is used less frequently. Complications of both phenol and alcohol include painful paresthesias and dysesthesias up to 32% in the 10% of the patients [35]. In a case series by Ko et al, pudendal nerve block with phenol solution used as a treatment for external urethral sphincter spasticity produced excellent results in 7 SCI patients [16]. In addition, pudendal nerve block with phenol solution has been proven an effective treatment for detrusor-sphincter dyssynergia in SCI patients [23]. It has been shown that ultrasound-guided obturator nerve block may treat bilateral adductor spasticity in paraplegic patients 25 and that subscapularis motor point block is a useful technique for spastic shoulders in patients with cervical SCI [24]. In another study, epidur-

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al anesthesia was used to minimize damage to a fresh tensor fasciae latae flap placed over a hip ulcer, in a SCI patient with severe muscle spasms [18].

Conclusions

Regional anesthesia techniques may be particularly useful in managing patients with SCI. They may be used in upper and lower limb surgery, abdominal surgery, and obstetrics and particularly for preventing autonomic dysreflexia. Moreover, they may be used for the management of chronic neuropathic pain and the treatment of spasticity in SCI patients. However, more high-quality studies are needed to clarify the benefits of regional anesthesia in the management and rehabilitation of SCI patients.

Conflict of interest

The authors declare no conflicts of interest

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Use of acupuncture in the rehabilitation of patients with spinal cord injury

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ABSTRACT

Although many patients surviving spinal cord injury (SCI) show some recovery in motor and sensory function below the initial level of injury, spontaneous recovery in patients with complete SCI is quite limited. However, there have been reports of patients improving with surgery, pharmacological interventions, and alternative medical approaches such as acupuncture. The purpose of this study was to review the use of acupuncture in the rehabilitation of patients with SCI. For this reason, a review of the current literature was performed using the online PUBMED database and the PRISMA guidelines. Inclusion criteria were human studies, studies written in English language, and studies that evaluated the use of acupuncture in the rehabilitation of SCI patients. Finally, 14 studies were included in the present review. There is emerging evidence that acupuncture may have a beneficial effect in the rehabilitation of SCI patients, particularly in terms of restoring motor and sensory function, and controlling chronic pain, neurogenic bladder and bowel and secondary osteoporosis. However, high quality studies are scarce. Further prospective, randomized, controlled studies are needed to fully elucidate the role of acupuncture in the rehabilitation of SCI patients.

Key Words: acupuncture, spinal cord injury, tetraplegia, quadraplegia

Introduction

Patients suffering from a spinal cord injury (SCI), face a variety of changes in motion and sensation, which negatively affect their quality of life. The degree of functional disability depends on the site and extent of injury. SCI, regardless the type, can lead to serious complications, including loss of motion, loss or alteration of sensation, respiratory insufficiency, loss of bowel or bladder control, excessive reflex activity or contractures and chronic pain due to spinal cord damage [1]. Although, nowadays, such lesions are irreversible, scientists are constantly working on the implementation of new therapies. These include nerve implants and medications that can promote nerve cell regeneration or improve function of the remaining intact nerves [2].

Despite the fact that many patients surviving a SCI show some recovery in motor and sensory function below the initial level of injury, spontaneous recovery in patients with complete SCI is quite limited. However, there have been reports of patients improving with surgery, pharmacological interventions, and alternative medical approaches such as acupuncture [3-4]. Acupuncture is a popular, complementary, mildly invasive, non-pharmacologi-

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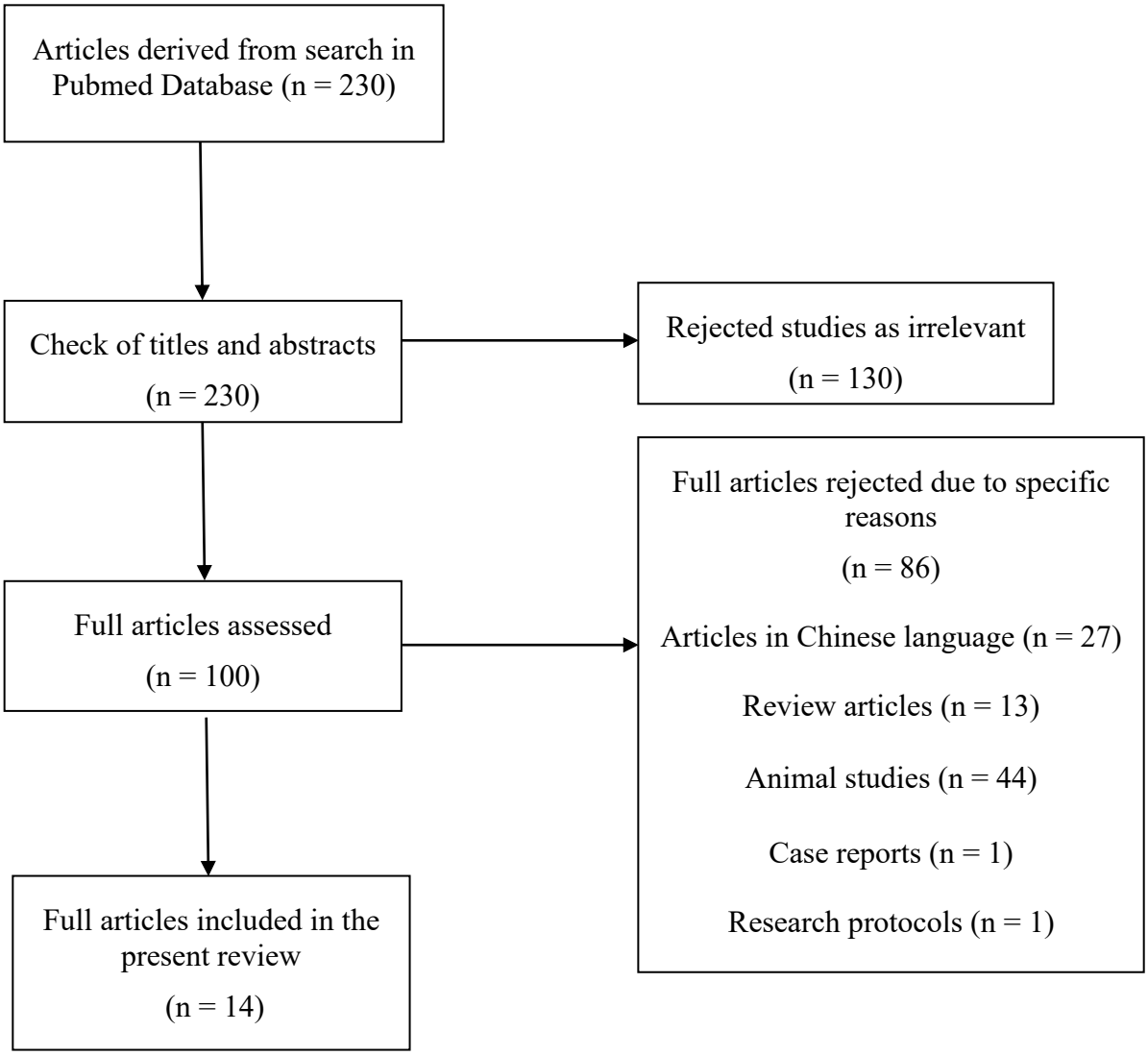

Table 1: Flowchart

cal therapeutic technique. It is used in controlling acute and chronic pain and in the rehabilitation of patients with sports injuries and neuromuscular diseases. There is plenty of evidence of a beneficial effect of acupuncture in patients with knee osteoarthritis, chronic low back and neck pain, migraines and chronic tension-type headaches, postoperative nausea and vomiting, pregnancy related vomiting, and infertility and in the reduction of side effects of chemotherapy and radiotherapy [5-8]. The purpose of this study was to review the use of acupuncture in the rehabilitation of patients with SCI.

A review of the current literature was performed using the online PUBMED database and the PRISMA guidelines, using the following key words: "acupuncture" AND ("spinal cord injuries" OR "spinal cord injury" OR "tetraplegia" OR "quadriplegia"). Inclusion were human studies, studies written in English language, and studies that evaluated the use of acupuncture in the rehabilitation of SCI patients. Studies in other than English language, animal studies, reviews, case reports, clinical protocols, studies that did not evaluate acupuncture and studies that did not involve SCI patients were excluded.

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Discussion

Primary search results included 230 papers. After reviewing titles and abstracts, 130 studies were rejected as irrelevant. Of the remaining 100 studies evaluated, 86 were rejected (27 studies in Chinese, 13 review studies, 44 experimental studies, 1 case report study and 1 research protocol). Eventually, 14 studies were included in this review (Table 1).

Experimental studies have shown that acupuncture contributes to the differentiation of stem cells into neuron-like cells and to the mobilization of CD133(+)34(-) cells in SCI patients [9-10]. Although the mechanisms of action of acupuncture in SCI patients are largely unknown, a few human studies have been published investigating the role of acupuncture in the rehabilitation of SCI patients.

Motor and sensory function

The beneficial role of acupuncture in the recovery of motor and sensory function after SCI has been investigated in a plethora of animal studies. Electroacupuncture has been found to influence neuronal apoptosis, inhibit astrogliosis, increase acetylcholinesterase activity and downregulate platelet-derived growth factor (PDGF), thus improving motor neuronal activity and recovery [11,12]. However, human studies are rare. In a prospective, randomized trial by Wong et al on 100 SCI patients, acupuncture was found to produce statistically significant improvement in sensory and motor scores one year after injury, in comparison to the control group [13]. Another case series showed no effects on heart rate variability of patients with complete SCI when a laser acupuncture was applied below the level of injury, in contrast with their healthy counterparts who showed the opposite pattern [14].

Chronic neuropathic pain

Several studies have shown the benefits of acupuncture in decreasing neuropathic pain intensity in SCI patients. In a randomized clinical trial including 24 SCI patients, an 8-week acupuncture regimen resulted in significant reduction in neuropathic pain [15]. Norrbrink et al, in a randomized trial on 30 SCI patients comparing a 6-week treatment with massage and acupuncture, reported that both acupuncture and massage may relieve neuropathic pain [16]. In a prospective, cohort study by Nayak et al, 22 SCI patients with moderate to severe pain received a course of acupuncture treatments for 7.5 weeks. About 46% showed significant improvement in pain intensity. However, 27% reported an increase in pain intensity lasting for at least 3 months. The authors concluded that the effect of acupuncture on neuropathic pain depends on the site and type of pain, as well as the type of SCI. Incomplete SCI patients have a better response in comparison to patients with complete SCI [8]. In a retrospective study on 36 SCI patients subjected to an electroacupuncture protocol, 2/3 of patients showed significant post-intervention improvement. The possibility of improvement after acupuncture was higher in cases of bilateral or symmetrical pain, burning and constant pain [17].

Shoulder pain

Chronic shoulder pain is a frequent problem for SCI patients using wheelchairs. A randomized, double-blind, placebo-controlled study in 10 SCI patients, showed that acupuncture may reduce shoulder pain by 66%, but no statistical significance was observed in comparison to the control group [18]. In another prospective clinical trial on 18 SCI patients with chronic shoulder pain who used manual wheelchair as their primary means of mobility, acupuncture was found to have equal analgesic effect with Trager Psychophysical Integration (type of manual therapy) [19].

Neurogenic bladder

Recently, acupuncture has gained popularity in the treatment of bladder dysfunction. Five clinical studies have been identified, investigating the effects of acupuncture on neurogenic bladder in SCI patients [20-23]. In a randomized, controlled trial by Cheng et al, acupuncture was found to be beneficial in the management of neurogenic bladder of SCI patients, and the earlier patients received electro-acupuncture therapy, the sooner the bladder balanced. On the other hand, acupuncture had no effect in patients with complete SCI and severe detrusor-sphincter dyssynergia or persistent areflexic bladder [20]. In another randomized, controlled trial, electroacupuncture was found effective in the treatment of urinary retention in SCI patients by increasing voided volume, promoting the balance of vesical function, and reducing residual urine

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volume and frequency of intermittent catheterization [21]. Another clinical trial on 13 SCI patients suffering from urinary incontinence showed that in patients treated with acupuncture, incontinence disappeared in 15% of cases and decreased in 50% of cases. Maximun cystometric bladder capacity increased significantly in the acupuncture group [22]. In addition, the authors of a prospective, observational study including 14 SCI patients, reported that acupuncture may decrease urinary incontinence and post-void residual urine volume, improving neurological detrusor underactivity [23]. Finally, in a prospective, randomized trial by Wong et al, including 100 SCI patients, acupuncture was found to produce statistically significant improvements in bladder control scores one year after the injury, in comparison to the control group [13].

Autonomic Dysreflexia

A prospective, cohort study evaluated the effects of acupuncture needle insertion above and below the level of SCI, in 15 SCI patients at risk for autonomic dysreflexia. Though systolic and diastolic blood pressures did not alter over 15 treatment sessions, 3 SCI patients experienced acute elevation of systolic blood pressure that suggested incipient dysreflexia. The authors suggested a careful monitoring of blood pressure in SCI patients receiving acupuncture treatment [24].

Neurogenic bowel

Two clinical studies were identified to investigate the effect of acupuncture in bowel dysfunction in SCI patients. In a prospective, randomized trial by Wong et al, including a total of 100 SCI patients, acupuncture was found to produce statistically significant improvements in bowel functional independence measures one year after the injury, in comparison to the control group [13]. In another prospective, observational study including 14 SCI patients, the authors noticed that after a 2-month acupuncture regime, 29% of patients resumed normal bowel movement and 36% of patients reduced the dependence on supplementary defecation methods [23].

Secondary osteoporosis

Secondary osteoporosis is a frequent complication of SCI, due to prolonged immobilization. In a randomized, controlled trial, the addition of acupuncture to standard anti-osteoporotic treatment led to increased bone mineral density; however, the difference was not significant [25].

Conclusions

There is emerging evidence that acupuncture may have a beneficial effect in the rehabilitation of SCI patients, particularly in terms of restoring motor and sensory function and controlling chronic pain, neurogenic bladder and bowel and secondary osteoporosis. However, high quality studies are scarce. Further prospective, randomized, controlled studies are needed to fully elucidate the role of acupuncture in the rehabilitation of SCI patients.

Conflict of interest

The authors declare no conflicts of interest

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