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Review

The history of biodegradable magnesium implants: A review ☆

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ABSTRACT

Today, more than 200 years after the first production of metallic magnesium by Sir Humphry Davy in 1808, biodegradable magnesium-based metal implants are currently breaking the paradigm in biomaterial science to develop only highly corrosion resistant metals. This groundbreaking approach to temporary metallic implants is one of the latest developments in biomaterials science that is being rediscovered. It is a challenging topic, and several secrets still remain that might revolutionize various biomedical implants currently in clinical use. Magnesium alloys were investigated as implant materials long ago. A very early clinical report was given in 1878 by the physician Edward C. Huse. He used magnesium wires as ligature for bleeding vessels. Magnesium alloys for clinical use were explored during the last two centuries mainly by surgeons with various clinical backgrounds, such as cardiovascular, musculoskeletal and general surgery. Nearly all patients benefited from the treatment with magnesium implants. Although most patients experienced subcutaneous gas cavities caused by rapid implant corrosion, most patients had no pain and almost no infections were observed during the postoperative follow-up. This review critically summarizes the in vitro and in vivo knowledge and experience that has been reported on the use of magnesium and its alloys to advance the field of biodegradable metals.

1. Introduction

The history of biodegradable magnesium implants started shortly after the discovery of elemental magnesium by Sir Humphrey Davy in 1808 [1]. His assistant, Michael Faraday, enabled the production of Mg metal by electrolysis of fused anhydrous $MgCl_2$ in 1833 [1]. The commercial production of Mg by electrolysis was realized by Robert Bunsen, who created a small laboratory cell for the electrolysis of fused $MgCl_2$ in 1852 [1]. At that time, Mg was produced in small quantities in America and Europe for pyrotechnical use, and as igniting bands or wires for flash lights of the upcoming photographic industry [1]. These initial Mg products were presented at the world exhibition in London in 1862 [1]. It is most likely that the physician Edward C. Huse used some of those Mg wires as ligatures to stop bleeding vessels of three human patients in 1878 [2]. He already observed that the corrosion of Mg was slower in vivo and that the time period until complete degradation was dependent on the size of the Mg wire used [2]. Huse wrote very enthausiastically about the degradable properties of the metal [2].

The most influential pioneer was the physician Erwin Payr from Graz, Austria whose versatile clinical applications and reports inspired many other clinicians to advance the field of biodegradable magnesium implants to various surgical areas (Fig. 1). He started his first experiments on Mg resorption in 1892 [3], but his main problem at that time was to get filigree fabricated devices made of Mg for his studies [3,4]. In 1898, Payr was supplied with pure Mg sheets and plates, pins, spheres, wires, pegs, cramps and nails from the company I. Rohrbeck in Vienna, Austria [3,4]. Around 1900, Payr already proposed that tissue oxygen and water content, carbon dioxide, the dissolved salts in blood and the chemical processes in cells were mainly responsible for the corrosion of Mg in vivo [3,4]. Albin Lambotte was also an early clinical investigator of biodegradable Mg and the mentor of his assistant Jean Verbrugge, who continued and extended the animal experiments and clinical studies [5–9]. An overview of authors who reported on the results on Mg for biomedical applications is given in Table 1. Since the problem of controlling the corrosion of Mg in vivo had not been sufficiently solved, many surgeons preferred to use the more corrosion-resistant V2A steel. Thus, Mg was no longer investigated intensively as a biomaterial [10]. These fascinating historic reports on various biomedical applications of metallic Mg in humans and animals are summarized in this review and structured

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Fig. 1. A portrait of Prof. Dr. Erwin Payr, the Austrian surgeon and pioneer in the field of biodegradable magnesium implants [37]. With kind permission from Springer Science + Business Media.

according to their clinical applications, along with the general findings of the in vitro and in vivo behaviour of Mg-based implants.[1]

2. History of magnesium production and possible origin of used magnesium

Sir Humphrey Davy, a British chemist, first isolated aluminium in 1807 and identified magnesium in 1808 [1]. Davy discovered many metals and their production processes [1]. Davy's assistant was Michael Faraday, who produced Mg metal by electrolysis of fused anhydrous $MgCl_2$ in 1833 [1]. Commercial production of Mg by electrolysis is credited to Robert Bunsen, the German scientist, who created a small laboratory cell for the electrolysis of fused $MgCl_2$ in 1852 [1]. The first Mg samples to be produced on an industrial scale were used mainly for pyrotechnical applications, and were presented at the world exhibition in London in 1862 [1]. At that time, small production lines of Mg for use in pyrotechnical and photographical applications were working in France, England and USA [1]. The commercial electrolytic magnesium production began in Germany in 1886, by using a modification of Bunsen's cell [1]. The Aluminium und Magnesium Farbik in Hemelingen (Germany) designed and built a plant for the dehydration and electrolysis of molten carnallite [1]. In 1896, this process was further developed by Chemische Fabrik Griesheim-Elektron, who transferred the process to its Bitterfeld works and became the main Mg producer in the world until 1916. Later Griesheim-Elektron became part of I.G. Farbenindustrie AG. Many magnesium alloys under the brand name Elektron were developed for technical applications, but were also used for biomedical applications (Table 1). Several smaller companies in the USA started the production of Mg before 1915, but only the American Magnesium Corporate and the Dow Chemical Company survived until 1925, and only the latter thereafter [1]. Smaller Mg productions were active from 1915 the 1940 in Italy and France [1]. In England, Mg production started in a small company in Wolverhampton around 1919, and at the beginning of 1937 the company Magnesium Elektron Ltd. started its still ongoing Mg production [1]. The purity of Mg and its alloys was mainly determined by the Mg source and the production process. Thus, the surgeons were mainly dependent on the available local Mg alloys or capabilities of the closest Mg supplier.

3. Magnesium in cardiovascular applications

3.1. Wires and other designs for ligature

In 1878, Huse used a Mg wire ligature successfully to stop bleeding vessels three times: once in a radial artery and twice in the operation for varicocele [2]. Huse suggested using Mg wires also for ovariotomy and haemorrhoids [2]. In 1900, Payr regretted that the available Mg wires were too brittle to be a suitable suture material [3]. Therefore, Payr investigated tubular, thin-walled Mg cylinders as connectors for vessel anastomosis [3,4]. In 1924, Seelig was inspired by the work of Payr, Chlumský, Lespinasse and Andrews when he was considering Mg for ligatures [11] – even though Andrews had stated that pure Mg wires cannot be tied in even loose knots, as it breaks immediately on kinking, and it cannot be twisted due to its brittle nature [12]. As had previously been reported by Payr [3], Seelig had found in 1924 that the available Mg wires on the market were too brittle [11]. However, Seelig was encouraged to continue his research by a technical report from the Bureau of Mines of the Department of the Interior [11]. The bureau suggested using pure Mg that had been produced by distillation in vacuum to obtain more ductile Mg wires (for mechanical properties see Table 2) [11]. Furthermore, it was suggested that noble metals be alloyed with Mg to increase its ductility (e.g. gold or silver) [11]. The report also emphasized that marked ductility can be expected only in alloys which are solid solutions of one component in another [11]. Seelig was working in close cooperation with the American Magnesium Cooperation (Niagara Falls, New York). This company supplied chemically pure Mg (99.99%), which was extruded and drawn into wire ranging from 0.005 inch upward. Seelig started his experiments as soon as he had pure Mg wires in his hand, but these first wires had a low tensile strength and were not sufficiently pliable. Retrospectively, Seelig's ambitious action was somehow premature, and led to inappropriate results and conclusions.

In 1935, Gotthard Gossrau, from I.G. Farbenindustrie AG, patented an Mg rope which consisted of a mesh of thin wires (less than 0.1 mm) around an inner stronger guiding wire or intertwisted wire bundle [13]. While the inner guiding wire bundle guaranteed the tensile strength of the rope, the outer wire mesh guaranteed the consistency of the inner bundle. The outer wire mesh provided an additional advantage of a better grip of the surgical suture material. By this invention, the usually observed low tensile strength and knot stiffness of Mg wires was overcome. The low tensile strength and known stiffness were usually obtained during cold work hardening in the production process.

The inventor Richard Jorgensen filed a patent on a modified haemostatic clip design in 1986 [14], inspired by the absorbable metal clips that E.W. Andrews had published in 1917 as a substitute for ligatures and deep sutures [12]. Andrews found that the use of absorbable Mg clips and staples speeds-up and ensures the safety of haemostasis. He recommended that the clips and staples be used for closing vessels, e.g. in the brain, or for closure of deep wounds, intestinal anastomosis and other applications [12]. Andrews liked the fact that the absorbable metals were not acting as permanent foreign bodies. Even though he found most of the investigated alloys and pure metals as unsuitable, Andrews still persued making alloys that were ideal for various implant applications [12]. He tried to improve the ductility, flexibility and tough-

[1] All parameters and units are reported as given in the original literature.