Original article

Anterior cervical fusion using magnesium-enriched hydroxyapatite: a two-year follow-up in 75 cases

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SUMMARY: Aims. *Anterior cervical discectomy and fusion is a surgery indicated to remove a herniated or degenerative disc in the neck. Numerous graft extenders are available on the market as alternatives to the patient's own autograft bone. Among all, calcium phosphate salts such as hydroxyapatite and β-tricalcium phosphate can be inserted in cages and allow vertebral fusion. Aim of the present study was to evaluate the safety and efficacy of a new generation biomimetic hydroxyapatite enriched with magnesium ions inserted in cages for spinal fusion.*

Materials and Methods. *A series of consecutive patients undergoing anterior cervical discectomy was selected to be treated with the use of an magnesium-doped ydroxyapatite bone graft material inserted in cage. Clinical and radiologic data were collected immediately after surgery, then up to 2 year after surgery. The primary endpoint (i.e. safety) was considered as lack of any adverse event leading to revision surgery or re-hospitalization during the follow-up period. The secondary endpoint (i.e. performance or evidence of fusion) was considered as lack of cage mobilizations recorded during the follow-up period.*

Results. *Seventy-five patients underwent interbody spinal fusion for the treatment of anterior cervical discectomy. A minimum 2-year follow-up was recorded for all the patients. Radiographic images showed the stability of the implant, as result of successful surgery. No adverse events (cage mobilization, infection, etc.) were recorded.*

Conclusions. *Mg-hydroxyapatite bioceramics show osteoconductive properties and a safety profile when employed in anterior cervical discectomy procedures.*

KEY WORDS: *Anterior cervical discectomy and fusion, Fusion, Magnesium-enriched hydroxyapatite.*

INTRODUCTION

Spondylosis is the general degeneration of the spine that can occur in joints, discs, and bones of the spine as we age. Conservative management, such as anti-inflammatories or physical therapy, is the preferred and often only required intervention. In unresponsive patients, surgery is indicated[8]. Anterior cervical discectomy and fusion is a surgery indicated to remove a herniated or degenerative disc in the neck.

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LIST OF ACRONYMS AND ABBREVIATIONS: **ACDF** = Anterior Cervical Discectomy and Fusion; **ANOVA** = ANalysis Of Variance; **BMI** = Body Mass Index; **CaP** = Calcium Phosphate; **HA** = HydroxyApatite; **Mg** = Magnesium.

This surgical procedure allows removing the damaged disc from the front (anterior) of the spine through the throat area. After the disc is removed, the space between the bony vertebrae is empty and a spacer bone graft is inserted to fill the open disc space and prevent the vertebrae from collapsing. The graft serves as a bridge between the two vertebrae to create a spinal fusion. The system "bone graft-vertebrae" are fixed in place with metal plates and screws. The instrumentation and fusion work together and, after 3 to 6 months, the bone graft should join the two vertebrae and form one solid piece of bone.

Bone grafts available to be used in ACDF can come from different sources. Typically, autologous bone is considered the "gold standard" choice, because of the osteogenic, osteoinductive and osteoconductive properties, which allow new bone formation[8,9,13,14], few incidences of graft complication and biocompatibility, no risk of disease transmission or immunogenic reactions[12]. However, drawbacks such as risk of harvest site morbidity, infection, hematoma, pelvic fracture, limitations with supply and others, can limit its use[14].

Among the possible graft alternatives available, synthetic bone grafts such as calcium phosphate derivatives and ceramics have been widely employed in fusion procedures, because of their biocompatibility, no risk of infection, the unlimited supply and, most important, the lack of donor site morbidity[7,13].

Based upon the natural occurring calcium salts and hydroxyapatite found in human bone, ceramics have been widely investigated for use in the cervical spine as well, showing good results in terms of fusion performance and clinical outcomes[6,15,29].

In the last decades, new generations HA-based biomaterials have been developed with superior properties, strongly influenced by the nature of components, the composition and the morphology. Calcium ions, phosphate ions, and hydroxyl groups can be replaced by other ions, and studies in animal models have demonstrated that HA-substituted ions enable the crystal cell structure of ceramic derivatives to become unstable and more biologically active, thereby promoting rapid cell-mediated material resorption, new bone formation and remodeling[23].

Magnesium is certainly one of the most important bivalent ions associated with biological apatite: it is one of the most abundant minerals in the human body and approximately 50% of Mg^{2+} is naturally present in the composition of bone tissue. Mg^{2+} enables the HA crystal cell structure to become unstable and more biologically active, promoting rapid cell-mediated material resorption, new bone formation and remodeling by cross-talking with progenitor cells at the molecular level[10,16,17]. Conversely, Mg^{2+} depletion affects all stages of skeletal metabolism, causing cessation of bone growth, decrease in osteoblastic activities, osteopenia and bone fragility. For all these reasons, Mg-HA has become of great interest in the development of effective bone substitutes[10,17]. In vitro experiments revealed an active interaction between Mg-HA biomaterials and human mesenchymal stem cells with an increase of cell metabolic activity[3,18], whereas preclinical studies in large animal models[5,24,27] demonstrated good osteointegration and the deposition of new bone tissue in spinal procedures.

In this panorama, an Mg-doped HA-based bone graft material (*SintLife, FinCeramica Faenza, S.p.A.*) has been employed in our institute for interbody spinal fusion procedures. In vivo animal models to assess spinal fusion with the device have shown that Mg-HA led to the deposition of new bone tissue without qualitative and quantitative differences as compared to newly bone formation with the use of autograft bone[5].

Due to the conspicuous casuistry of patients treated at our Institution with the above-mentioned biomaterial, the present retrospective case series aims to demonstrate the safety and efficacy at 2 years follow-up of the Mg-HA doped SintLife as bone graft substitute inserted in cages for cervical interbody fusion.

□ AIMS

Aim of the present study was to evaluate the safety and efficacy of a new generation biomimetic hydroxyapatite enriched with magnesium ions inserted in cages for spinal fusion.

□ MATERIALS AND METHODS

■ **Patient population.** This is a retrospective case series of patients undergoing ACDF with the use of

an Mg-doped HA bone graft material inserted in cage at the Department of Neurosurgery, "Santa Maria delle Grazie" Hospital in Pozzuoli, Naples, Italy, between 2017 and 2019. Data were gathered through the review of patients' case notes and relevant data records. Patients were evaluated preoperatively: baseline characteristics (age, gender, BMI), smoking habits, and previous surgical procedures undertaken) were recorded before surgery. No inclusion or exclusion criteria were selected.

■ **The device description.** SINTlife is a Class III, new generation biomimetic hydroxyapatite enriched with magnesium (Mg^{2+}) ions and with a chemical and physical composition equivalent to the mineral constituent of human bones. Thanks to the specific biomimetic chemical composition and the micro-structural properties, SINTlife promotes new bone formation, high osteointegration kinetics and resorbable properties. The device, in form of putty, can be easily handled and stabilized in bone cavity sites. SintLife remains in situ for the time required for bone growth and maturation and, while sustaining osteoprogenitor cells remodeling, it resorbs over a physiologically appropriate period (6 to 18 months). As such, fast osteointegration kinetics of magnesium-enriched hydroxyapatite lead to a faster bone formation.

■ **Surgical procedure.** All surgical procedures were performed by the same senior surgeon using open anterior approach to the cervical spine. Patients were preoperatively treated with intravenous antibiotic treatment. All patients underwent decompression and spinal stabilization with the use of instrumented fixation supports (pedicle screws/rods) in addition to bone graft material (*SintLife, FinCeramica Faenza S.p.A., Faenza, Italy*).

SintLife was placed in titanium cage prior to its placement. The cage was then placed in the interbody space to allow bony fusion. In all the cases, the cage was compressed, in order to reproduce the normal inward lordotic curvature of the spine column. The wound was sutured in three layers over two suction drainage tubes. The patients were intravenously treated with prophylactic antibiotic therapy immediately after surgery and mobilized 2 to 3 days after surgery.

■ **Results assessment**. Clinical and radiologic data were collected immediately after surgery, then up to 2 year after surgery. The primary endpoint (i.e. safety) was considered as lack of any adverse event leading to revision surgery or re-hospitalization during the follow-up period. The secondary endpoint (i.e. performance or evidence of fusion) was considered as lack of cage mobilizations recorded during the follow-up period. The secondary endpoint (i.e. evidence of fusion) was considered achieved if, during the follow up period, no mobilization of cages was reported, which is possible only in case of bone graft performing fusion.

■ **Statistical analysis.** Values are presented as mean values, minimum and maximum ranges, ratios or percentages, as appropriate. Analysis was performed with the use of the Friedman ANOVA test for comparisons among the two treatment groups. The level of statistical significance was set at $P < 0.05$. Data were analyzed with the use of Statistica 6 software (*StatSoft Inc, Tulsa, Oklahoma, USA*).

□ RESULTS

Between 2017 and 2019, 75 patients underwent interbody spinal fusion for the treatment of degenerative disc diseases at the Department of Neurosurgery, the Santa Maria delle Grazie Hospital in Pozzuoli, Naples, Italy. A minimum 2-year follow-up was recorded for all the patients. There were 45 male and 30 female (ratio 1,5:1), mean age 54 years (age range 28-79). Main aetiology was degenerative (74/75 cases, 98.7%) and only was case was treated because of traumatic causes. None of the subjects had smoking habits. Patients were operated for ACDF, all the patients received a Mg-HA based graft material inserted in cage. The majority of patients (40, 53%) underwent 1 level of fusion, 26 underwent 2 levels of fusion, 9 patients had 3 fusion levels.

At follow-up period, radiographic images showed the stability of the implant, as result of successful surgery and fusion processes taking place. No adverse events (cage mobilization, infection, etc.) were recorded.

□ DISCUSSION

The purpose of a spinal fusion (arthrodesis) is to link or weld bones together. Many spinal conditions cause instability and/or pain (e.g., degenerative disc disease, scoliosis, trauma, infection and neoplasia) and require treatment with a spinal fusion[21]. Among the different possible approaches, interbody fusion is an established treatment aimed at removing a disc that is the source of back or leg pain, and fuse spinal vertebrae with the addition of bone grafts. Anterior cervical discectomy and fusion is a type of neck

surgery that involves removing a damaged disc to relieve spinal cord or nerve root pressure and alleviate corresponding pain, weakness, numbness, and tingling. A fusion surgery is performed at the same time as the discectomy operation in order to stabilize the cervical segment. The fusion procedure involves placing bone graft and/or implants where the disc originally was in order to provide stability and strength to the area.

Bone grafts can be divided into three main categories (autologous bone, allograft bone, synthetic bone grafts) based on where they are obtained (the patient's own bone, bone obtained from cadavers and sterilized for use, synthetic products that either assist or replace the need for autograft or allograft bone in a spine fusion, respectively). The choice of which type of bone graft to use is largely dependent upon where the fusion is done in the spine (in the cervical, thoracic, or lumbar spine), the surgical approach to the fusion (anterior or posterior) and the availability materials. Autograft bone (usually harvested from the iliac crest) is considered the "gold standard" material to provide fusion. In ACDF, a mean arthrodesis rate of 77% is reported[31]. In one-level non-instrumented procedures, autograft fusion rates are a reported 83-99%[26], but decreases with number of levels fused. Autologous bone shows relatively few incidences of graft complication, such as graft collapse or migration, and it is biocompatible, posing no risk of disease transmission or immunogenic reactions. Nonetheless, drawbacks related to the harvesting procedures are reported. In a retrospective study of one-level ACDF, Silber and colleagues found 26.1% of patients suffering from persistent pain and 15.7% experienced numbness at the harvest site[28]. Functional assessment revealed impairment in ambulation (12.7%) and other daily activities. A 30% of donor site pain is also reported[25], which caused patients to have longer hospital stay. Finally, the limited supply can affect its use, on behalf of synthetic materials, which unlimited quantity and evolution during decades (to provide safety profiles) has allowed their ordinary use in common clinical practice of spinal procedures. Among the synthetic bone grafts (also known as "bone graft substitutes"), ceramic derivatives like calcium phosphate and hydroxyapatite have been employed in ACDF. Kim et al.[15] reported good clinical results and solid fusion at 1 year follow up in a patient population of 70 subjects operated for ACDF with a 30% porous HA graft. No graft collapse was reported, encasement of the implant and formation of union were observed. Bruneau and colleagues[6] showed complete fusion occurred in 98% of one-level and 100% of two-level procedures in a clinical study employing HA in ACDF. Thalgott et al. reviewed 26 patients who received coralline HA with rigid plating for ACF[30], showing no graft complications and 100% of grafts incorporation at 36 months follow-up. Coralline HA inserted in carbon fiber cages showed complete fusion at 12 months with no complications, in one- or two-level procedures[1]. A prospective randomized trial by McConnell et al., which compared coralline HA with autograft, showed significant clinical improvement and similar fusion rates (HA 78%, autograft 79%) at 24 months follow-up[20].

In the present study, we show the performance of a Mg-doped HA (named SintLife) to achieve bony fusion, as manifested by radiographic images. Previous in vitro experiments demonstrate chemotactic activities[3,18], new bone formation and good osteointegrative properties in spinal procedures[5,24,27], supporting its use in clinical practice.

In the present study we also show the safety profile of SintLife employed in ACDF procedures, confirmed by the lack of adverse events (i.e. inflammatory reactions or infections, cages mobilization, patients' morbidity) recorded in the follow-up period (2 year), as previously reported in literature by others[2].

According to current literature[11,19], bone graft substitutes with strong bioactive features may give rise to inflammatory reactions. Mokawem et al.[22] reported a 9.7% complication rate with the use of a Si-doped CaP bone graft packed in spinal fusion procedures, with some cases requiring revision surgery. Worst results were provided by Bolger[4], which reported a 30% complication rate with the use of Si-CaP in PLF procedures. 7% of the events were related to the device and required revision surgery, suggesting that some ions-doped bioceramics shall give rise to complications, as compared to CaP-based materials without ions augmentation.

In the present work, we show no inflammatory reactions following the use of Mg-HA in ACDF, highlighting the safety profile of the device when used in conjunction with cages.

□ CONCLUSIONS

SintLife, an hydroxyapatite bioceramic enriched in magnesium, has shown osteoconductive properties and a safety profile when employed in ACDF procedures.

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