Orthogem TriPore® HA and Bone Marrow Aspirate used in lumbar spinal fusion: 12 month clinical and radiological review

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ABSTRACT

Study Design: A prospective cohort study.

Objectives: To assess the efficacy of TriPore HA with bone marrow aspirate (BMA) as a substitute for autologous iliac crest bone graft in lumbar spine fusions and to compare the clinical and radiological outcome to results obtained in animal studies.

Summary of Background Data: TriPore HA is a new synthetic resorbable hydroxyapatite bone graft substitute with a unique three pore configuration, comprising of totally interconnected macropores, midipores and microspaces. The midipores, which are unique to TriPore, allow uniform distribution of osteocytes throughout the ceramic structure facilitating early osseointegration and remodelling.

Preclinical studies in a sheep femoral condyle model demonstrated that cylinders of TriPore HA were replaced by bone over time with minimal soft-tissue in-growth and excellent peripheral bone attachment.

TriPore gained European regulatory approval in 2006 and the present study represents the first report of its use in humans.

Methods: From August 2006 to November 2006 ten patients undergoing lumbar spinal fusion had TriPore HA and BMA used as a substitute for autologous iliac crest bone graft. Clinical and radiographic evaluation continued prospectively for twelve months. Results were based on clinical outcome assessment tools (Oswestry Disability Index – ODI, The Low Back Outcome Score – LBOS and a Patient Satisfaction Evaluation – PSE) and stringent radiological criteria for fusion.

Results: Nine patients had a successful outcome clinically and radiographically and one had a poor outcome clinically without good radiographic evidence of fusion. Using the disease specific outcome tools, for all the patients, there was a mean improvement of 40.5 points in the ODI and 43 points improvement in the LBOS, both results considerably above the level of "minimum clinical difference". The subjective PSE showed that five patients had complete relief of pain, four had good relief and one no relief of symptoms. In the nine "successful" patients all operated levels were radiographically fused with progressive conversion of TriPore HA to bone over the twelve month follow-up period.

Conclusions: The search for alternatives to iliac crest autograft has lead to a bewildering number of substitute bone grafts.
Many are expensive.

Some are associated with immunological and infective complications.

Few are sufficiently osteogenic to allow them to be routinely used by themselves in lumbar spine fusion. This pilot study has shown that TriPore HA shows great promise as a viable alternative to autograft when used with BMA. It is not as expensive as the rhBMPs nor does it have their potential immunological side-effects. There is no risk of infectious complications with TriPore HA unlike demineralised bone matrix preparations. Unlike other preparations of HA, TriPore HA is completely resorbed and the subsequent bone graft is remodelled which means that the risk of mechanical failure of the graft is much less than with incompletely resorbed HA formulations.

The preparation of the graft using TriPore HA and BMA is straightforward and is not associated with any device related complications. The clinical and radiological outcomes are equivalent to those found in the literature for autograft fusions, but there is no risk of the morbidity associated with the harvest of autograft.

Further longer-term follow-up will be needed to establish the credentials of TriPore HA beyond doubt, but the early results in this study are highly suggestive that TriPore HA is a viable alternative to autograft in lumbar fusions.

Key Points:

- TriPore HA is a unique formulation of hydroxyapatite and is the first to show reliable resorption in lumbar spine fusions.
- The clinical results of this study support the use of TriPore HA as an alternative to iliac crest autograft in lumbar fusions.
- TriPore HA is readily available, easy to use and there have been no device related complications associated with its use.
- The complications associated with autograft harvest are avoided when TriPore HA and BMA is used as the graft material.

Key words:

- bone graft substitute,
- hydroxyapatite,
- resorbable,
- TriPore,
- lumbar spine fusion.

INTRODUCTION

Spinal fusion to treat symptomatic spondylolisthesis or carefully selected cases of degenerative disc disorders of the lumbar spine has become established as a valid treatment over the past twenty years. The biological aim of fusion is to eliminate intervertebral movement by creating a solid arthrodesis. This requires meticulous fusion bed preparation, bone grafting and almost always, supplementary internal fixation. There is no doubt that autologous cancellous bone is the ideal graft material, but its harvest is associated with significant morbidity for many patients.[1,2,3,4,5,6,7] As a consequence, there has been extensive research activity during the past three decades, aimed at producing substitutes for iliac crest graft that are effective, cost efficient and avoid graft harvest morbidity.

For a material to be successful as a bone graft it should be osteoconductive and osteoinductive *(osteogenic)*. It may be possible to achieve this in one preparation such as high-concentration demineralised bone matrix, but most effective bone graft substitutes are combinations of conductive materials and inductive agents.[8] There is an extensive range of graft substitutes now available ranging from simple ceramics through collagen sponges to allograft preparations and most expensively, recombinant bioactive molecules. However, the ideal graft substitute that combines cost-efficiency and utility still remains elusive.

Calcium phosphate ceramic preparations are the closest structural and chemical mimics of the osteoconductive elements of human bone. The commonly used forms are tricalcium phosphate (TCP), hydroxyapatite (HA) and combinations of the two (biphasic preparations). HA is attractive as it is the closest ceramic in chemical and physical form to bone, but in the past it has not been possible to prepare HA that is reliably and progressively resorbed to be replaced by remodelled bone. As a result many researchers and clinicians consider that HA is unresorbable. TriPore HA, developed by Orthogem, has overcome this technical hurdle. It is resorbable and forms bone with little soft-tissue invasion.[9,10]

TriPore HA has a unique multi-porous structure consisting of a distinct three pore configuration: microspaces (4-10μm diameter), midipores (50-100 μm diameter) and macropores (300-800 μm diameter). Pore interconnectivity occurs throughout the whole structure which acts more like a scaffold than a simple porous material. Once TriPore HA has been soaked in autologous bone marrow aspirate the osteoconductive scaffold is transformed into a potent bone graft substitute. The three pore structure ensures a homogenous osteocyte density to the whole graft area which is considered to be essential in replicating the function of autologous cancellous bone in a bone graft site. Preclinical trials of TriPore HA, carried out in a sheep femoral condyle model, were successful in demonstrating mature bone formation throughout the implanted ceramic cylinders with matched resorption of the HA over a two year period.[9,10] As a result, TriPore HA was approved for use as a resorbable bone graft substitute in Europe, in contradiction to the commonly accepted view that HA is not resorbable.

METHODS

The study group consisted of ten patients undergoing lumbar spinal fusion between August 2006 and November 2007. It consisted of 10 patients, 4 males and 6 females, with a median age of 51 (range 39-78 years). All patients were operated upon by the senior author to ensure uniformity of technique.

The indications for surgery were spondylolisthesis – 4 patients; degenerative lumbar scoliosis – 2 patients; symptomatic degenerative disc disease at one or two levels – 3 patients; extension of a previous fusion due to symptomatic adjacent level degeneration – 1 patient.

The surgical procedures were: instrumented postero-lateral instrumented fusion (PLF) – 4 cases; transforaminal lumbar interbody fusion (TLIF) – 2 cases; posterior lumbar interbody fusion (PLIF) – 1 case; anterior interbody fusion (ALIF) – 1 case; anterior and posterior fusion (3600 fusion) – 1 case; uninstrumented PLF (UPLF) – 1 case.

All procedures with the exception of one (UPLF) were stabilised with pedicle screw instrumentation and the interbody fusions with appropriate cages.

There were 20 levels of fusion in the ten patients – 4 patients with a single level and the remaining 6 at multiple levels. L4/5 was the most common level followed by L5/S1 (Table 1).

All patients included in the study were non smokers. They were all investigated pre-operatively with plain x-rays, MRI scans and where indicated with provocative discography. The decision to offer surgery was made after aggressive non-operative treatment lasting at least six months had failed to control symptoms and disability remained significant. In addition patients were screened for psychosocial distress and non-physical dysfunction using an assessment based on the Waddell abnormal illness behavior criteria.[11]

Patients were not considered for surgery if they;

- had a body mass index of greater than 35,
- were involved in ongoing litigation for any musculoskeletal complaint,
- were medically retired due to back pain,
- had metabolic bone disease including osteoporosis,
- had evidence of skeletal malignancy including spinal secondaries,
- had local or systemic infections and ongoing treatment with medications such as systemic steroids and chemotherapy agents which could interfere with fusion.

The surgical technique in each case was standard for that procedure. The spine was exposed through a midline or para-median (Wiltse) exposure. Pedicle screw instrumentation and interbody fusion devices were implanted as appropriate. The postero-lateral fusion beds were prepared by meticulous decortication of the transverse processes, pars interarticularis and lateral aspects of the facet joints. TriPore HA was mixed with BMA aspirated with a Jamshidi needle from the posterior iliac crest through the main incision. BMA was aspirated in 3 ml aliquots to prevent venous blood dilution. 6 ml of BMA were mixed with each 10ml pot of TriPore granules and these mixtures were allowed to stand for at least 20 minutes before implantation to allow complete wicking of the BMA into the ceramic matrix.[12] In cases where autograft has been used as a graft material in the past, it has been harvested from the posterior iliac crest through the main incision and mixed with local decompression bone before implantation in the fusion bed. In this study, the TriPore/ BMA mixture was mixed with any local bone that was available (e.g. decompression bone in TLIF/PLIF cases) and was carefully delivered to the fusion site in a fashion designed to optimise graft/host bed surface contact.

Serial follow-up was carried out at 3, 6 and 12 months from surgery, which involved a clinical examination and radiological assessment.[12,13,14,15] At the same visit the patients underwent a detailed clinical enquiry by the junior author and completed three outcome questionnaires – the ODI,[16] LBOS,[17,18] and PSE,[19,20] not in the presence of the senior author.

Radiological evaluation consisted of supine antero-posterior and lateral x-rays of the lumbar spine at 3 and 6 months and standing views at 12 months after operation. Radiological assessment of interbody fusions was made in accordance with the 7 criteria of Brantigan and Steffee.[15] The evaluation of postero-lateral intertransverse fusions was determined by the presence of a solid continuous mass of bridging trabecular bone with no intervening radiolucent areas between the transverse processes and the absence of implant loosening as well as evidence of progressive conversion of the TriPore HA ceramic to bone.

RESULTS

All 10 patients in the study were available for regular serial follow-up evaluation over a 12 month period. On analysis of the data, 9 were deemed successful with 1 failure.

The median pre-operative ODI was 45.5 (range 12-70) falling to 5 at the 12 month follow-up (range 0-42). The minimum clinical difference appropriate for a surgical intervention for back pain using the ODI is 14. As a result the results for this group fulfilled the criterion of success according to this disease-specific outcome tool.

The median LBOS score pre-operatively was 24.5 (range 8-66). This rose to a median score of 67.5 (range 23-75) after surgery (Figure 1).

The one patient who was subjectively and objectively a failure of treatment had only an 8 point improvement in her ODI and 3 point improvement in her LBOS scores.

The subjective, generic Patient Satisfaction Evaluation (PSE) questionnaire revealed that five patients had complete relief of their symptoms; four had good relief and one had no relief of symptoms (Figure 2). On this score, like the ODI and LBOS, nine out ten patients had a successful outcome.

The successful group of nine patients underwent a total of 17 levels of fusion. Serial x-rays showed progression to fusion across all instrumented levels in these patients over the 12 months. There was clear evidence of TriPore HA resorption progressively in all nine patients with replacement by bone, as the animal studies had demonstrated (Figures 3-6).

In the patient deemed a clinical and radiological failure, little evidence of new bone was present on the 12 month follow-up x-rays and there was virtually no resorption of the TriPore HA.

There were no complications attributable to the use of TriPore in this series of patients. None had symptoms attributable to bone marrow aspiration. Two patients needed revision of TLIF cages within three months of the primary surgery as a result of migration secondary to cage design. Despite this, the TriPore graft worked well in both cases.

DISCUSSION

In this study of 10 patients treated with TriPore HA and BMA as a substitute for iliac crest cancellous autograft nine had a successful clinical and radiological outcome indicating that TriPore HA and BMA is a suitable alternative to autograft in lumbar spine fusion.

The lumbar spine poses a challenging environment for obtaining bony fusion especially with regards to the posterolateral spine. While autologous bone graft has been the material of choice, it is associated with significant donor site morbidity[1,2,3,4,5,6,7] and there is a limited quantity of it. This has led to a search for alternative sources of bone graft material. Many bone graft substitutes are available commercially and are broadly grouped on the basis of their origin as: bioactive ceramics, allografts, collagen sponges and bioactive molecules. Allografts carry the potential risk of disease transmission and immune reactions, while bioactive molecules are currently prohibitively expensive for routine use in most health economies.

Bioactive ceramics are osteoconductive matrices which possess several advantages in that they are non-toxic, non immunogenic, easy to sterilise and available in virtually unlimited supply. Tricalcium phosphate (TCP) is resorbed quite quickly, but suffers from variable bony replacement as a result. Hydroxyapatite (HA) has traditionally been considered as unresorbable which leads to problems such as incomplete osseointegration of the ceramic with the host bone and a risk of subsequent osteolysis secondary to an inflammatory response to retained ceramic particles. This can lead to reduced shear strength and fracture resistance within the implant and structural failure. To try to get the best from both preparations combinations of the two have been used (biphasic ceramics), however these still are likely to lead to non-resorption of the HA if it is manufactured in its traditional form. The main reason for this is that all conventional synthetic HA preparations lack connectivity between their pores through the "thick connecting wall" so impeding early osteocyte population. It is widespread population of the ceramic matrix with osteocytes that allows early and abundant bone formation over the ceramic surfaces so preventing soft-tissue in-growth and allowing early remodelling of the whole construct to mature bone with good mechanical properties. If there is a failure of widespread cell seeding within the ceramic, osseointegration is impeded resulting in a failure of bone formation on the ceramic surfaces and eventually this leads to mechanical failure of the implant.[21]

Therefore the main drawbacks of pre-existing ceramic composites were the lack of connectivity between their pores, their inability to attract, retain and uniformly incorporate osteocytes in the ceramic matrix and their inability to be adequately resorbed.

This led Orthogem to develop the TriPore HA, with its unique three pore configuration consisting of micropores, midipores and macrospaces, thus setting it apart from the other commercially available HA preparations (Figures 7a-c). The rationale of the TriPore HA design is the strategic placement of its porous structure. It consists of microspaces which are formed between ceramic particles with high surface free energy. Individual micro-plates of ceramic are joined to their neighbours at the junction of their sides rather than along their sides leading to point fusion. As a result, microspaces are created into which bone cells are attracted thus ensuring uniform osteocyte distribution throughout the graft material. In addition, the microporous structure is supportive of the osteocyte lacuno-canalicular organisation which mediates mechano-sensing within the new bone mass. This allows the release and accumulation of cellular growth factors essential for the ultimate timely resorption and replacement of the synthetic scaffold. The critical placement of the midipores within the walls of the macropores eliminates the 'thick connecting wall' commonly found in many SBGs that so often impedes the process of resorption. They also aid in nutrient flow and encourage osteoblast migration to form osteocytes in the microspaces. The macropore orientation in turn aids organisation of gross lamellar bone formation.

The process of conversion of the osteoconductive matrix to an osteogenic medium is achieved by the addition of BMA obtained from the posterior iliac crest.[8,12,13,14] The principles underlying this phenomenon was discovered by Marshall R. Urist in the 1960's, as the 'Principle of Bone Induction'.[22] He stated that BMA contained mesenchymal stem cells which in the right medium differentiated into pro-osteoblasts – a process known as bone marrow osteogenesis.

The results of this study have indicated that locally harvested growth factors and undifferentiated mesenchymal stem cells, in the form of bone marrow aspirate, evenly distributed onto a favourable construct, have the desired result of obtaining a sound radiological fusion with favourable clinical results.

The results of the preclinical studies of TriPore HA in sheep, revealed a better ratio of bone to residual ceramic and a greater peripheral bone attachment with a significantly lower soft tissue to bone ratio, when compared to a market dominant product like "Vitoss"(beta TCP).[1] The clinical significance of the presence of soft tissue within the ceramic graft substitute is indicative of macrophage mediated tissue degradation. This is not part of the bone forming cycle which includes osteoblast deposition of woven bone that is remodelled to lamellar bone by sequential osteoclast resorption and further organised osteoblastic osteoid deposition. With a comprehensive replacement of the ceramic with bone, the risk of implant failure is much reduced increasing the likelihood of a good clinical outcome.

The single failure in this patient group was predominantly attributable to the lack of stability over the length of the construct, secondary to a failure to instrument the segments. This arose as a result of adverse pedicle anatomy that was not apparent pre-operatively. As a result, the TriPore HA, which does not possess any intrinsic mechanical supportive properties, was unable to osseointegrate and subsequently form a solid fusion mass leading to the failure.

Although the authors early results with the TriPore HA have been encouraging, they recognise that the size of the sample group is small and that a further, long-term evaluation, will be needed before a full assessment of the efficacy of TriPore HA can be made. At this stage however, there is enough evidence to allow the authors to suggest that TriPore HA with BMA is a suitable substitute for autologous cancellous bone graft in lumbar spinal fusions.

TABLES & FIGURES

Patient	L2/3	L3/4	L4/5	L5/S1	Total
1			1	1	2
2			1		1
3		1	1	1	3
4		1	1	1	3
5				1	1
6		1			1
6			1		1
8	1	1	1		3
9		1	1	1	3
10			1	1	2
Total	1	5	8	6	20

Table 1

Distribution of fusion levels amongst the ten patients.

Figure 1 Serial ODI & LBOS measurements

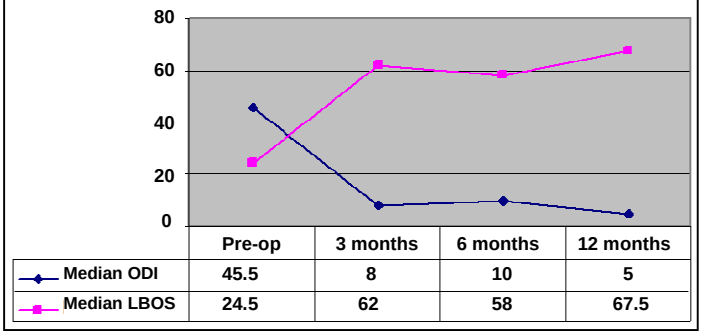
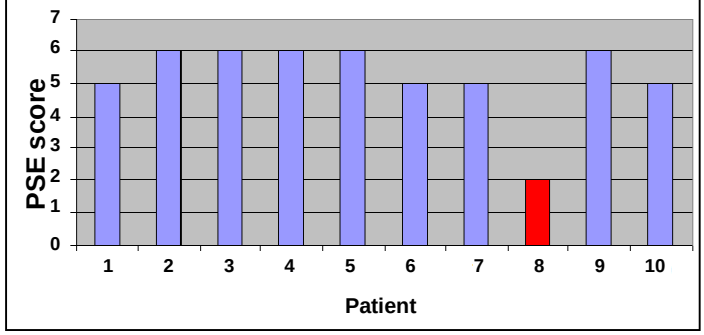


Figure 2 Patient Satisfaction Evaluation



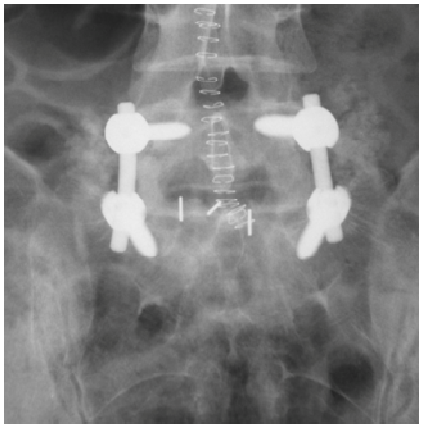


Figure 3

AP x--ray of a patient who had a TLIF at L5/S1 – immediate post--operative view showing granular appearance of TriPore HA graft in the postero--lateral position.

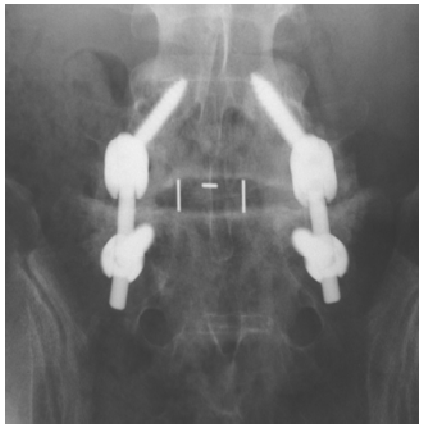


Figure 4

AP x--ray of a patient who had a TLIF at L5/S1 – 6 months post-operative view showing progressive conversion of TriPore granules to bone.

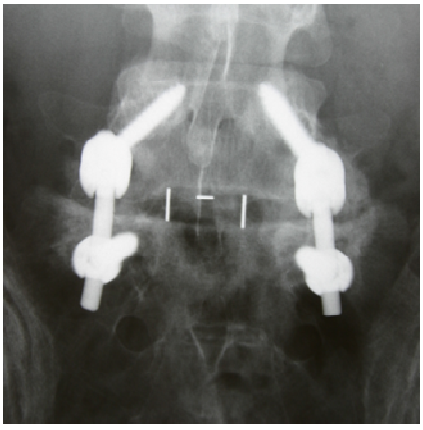


Figure 5

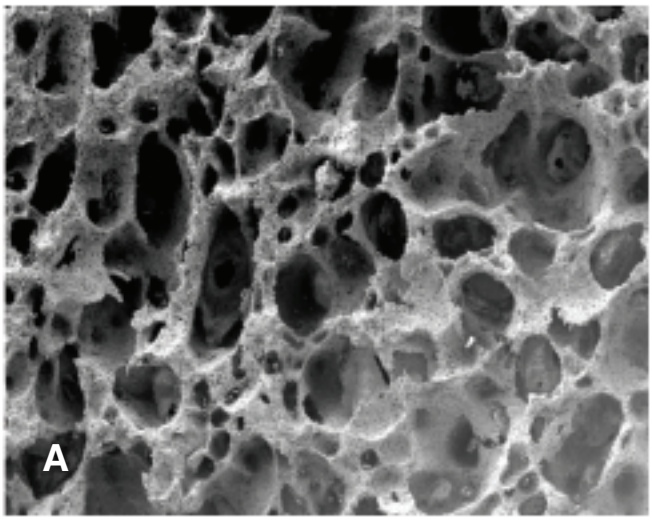
AP x--ray of a patient who had a TLIF at L5/S1 – 12 months post-operative view showing complete conversion of TriPore to mature fusion bone.

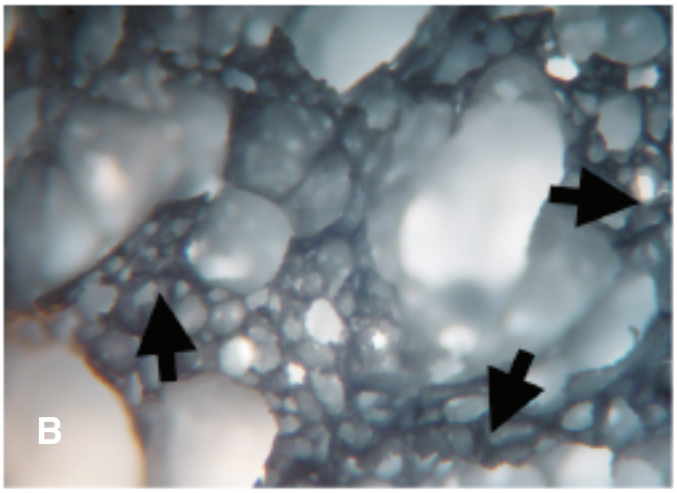
Figure 6

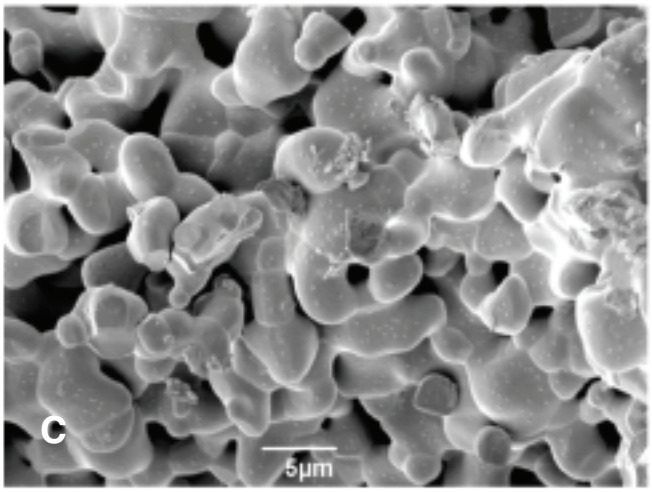
(A) *Interconected macropores. (SEM)*

(B) *Back Lit optical microscopy showing midipores within the connecting wall.*

(C) *Microspaces among the annealed ceramic particles. (SEM)*







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