Development and clinical cases of injectable bone void filler used in orthopaedic

G. Daculsi a,b, M. Durand a,∗, T. Fabrec, F. Vogtd, A.-P. Uzel b,e, J.-L. Rouvillain f

Original article

Abstract

This study reports several clinical cases for orthopaedic bone regeneration using an injectable bone substitute (MBCP Gel®) to demonstrate its safe use and efficiency in clinical applications. The biomaterial is a composite of microporous bioceramic hydroxyapatite granules that are associated with beta tricalcium phosphate (MBCP) and a synthetic hydrosoluble polysaccharide hydrogel (CE mark 123 and FDA dental domain registered). The present exploratory study demonstrated the generative osseous performance of this injectable bioceramic for filling various orthopaedic bone defects. The clinical cases showed bone ingrowth into the cavities created by drilling when removing the aseptic osteonecrosis of the femoral head during biopsy taking. Furthermore, bone reconstruction was seen after filling large cystic defects, at the time of the revision surgery of the hip prosthesis. Resorption and bone ingrowth with trabecular bone architecture were observed in defects created in long bones (femur and tibia). Patients were followed during 5 months to 1 year. The overall results demonstrated the safe use and the clinical performance of this Injectable bioceramic in orthopaedics.

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Résumé

Cette étude présente plusieurs cas cliniques de régénération osseuse en orthopédie démontrant la sécurité et la performance du substitut osseux injectable MBCP Gel®. Ce biomatériau est un composite associant des granules de phosphate de calcium biphasés microporeux (hydroxyapatite et bêta tricalcium phosphate) et un gel hydrosoluble synthétique polysaccharidique (CE 123 et FDA). Les cas cliniques présentés ont démontré la performance du MBCP Gel® pour remplir des défauts osseux orthopédiques divers. Les cas cliniques montrent une régénération osseuse dans les cavités osseuses créées lors du forage réalisé dans les ostéonécroses aseptiques de la tête fémorale, et dans le comblement de défaut kystique et de révision de prothèse totale de hanche. Le suivi clinique de cinq à douze mois montre une résorption du biomatériau et une régénération osseuse aux dépens du composite.

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1. Introduction

Synthetic hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP) became commercially available as bone substitute materials for dental and orthopaedic surgeries [1], primarily through the pioneer work performed by Jarcho and de Groot and their co-workers in the early 1980s [2,3]. The first basic studies on biphasic calcium phosphate (BCP) with varying HA/β-TCP ratios were reported by Daculsi, LeGeros, and their co-workers [4–7], demonstrating various bioactivities of these ceramics when manipulating the HA/β-TCP ratio. Subsequently, focused studies on BCP by Daculsi

∗ Corresponding author.
E-mail address: marlene.durand@chu-bordeaux.fr (M. Durand).
et al. [8,9] have shown promising results and therefore led to a significant increase in the use of commercial BCP bioceramics as bone substitute materials for orthopaedic and dental applications [10–16].

More recently, BCP granules were used for the development of a new generation of injectable bioceramic, and/or mouldable bone substitutes [17,18]. BCP granules can be combined with various polymers of natural (e.g., fibrin sealant, Tricos™ combination of BCP and fibrin sealant as bone substitute biomaterials), or synthetic origin (e.g., hydrosoluble polymer) [19–21].

The granulated form already showed their osteoconductive capacity in various sites. These granules are however difficult to use and keep in more exiguous sites. Using injectable or mouldable composite materials make it possible to obtain a plastic material suitable to fill osseous cavities of whatever shape. MBCP Gel® is an injectable biomaterial consisting of BCP granules associated with a hydrosoluble polymer that is not self-hardening. This material has been shown to be biocompatible and potentially resorbable. Thanks to its initial plasticity, it assumes easily the shape of the bone defect to eliminate any shaping of the material, particularly with blood arrival/support in the defect site that favours haemostasis. MBCP Gel® does not have mechanical properties like the hydraulic bone cements [20]. However, bone cells are able to invade the spaces released by the disappearance of the polymer carrier. Bone ingrowth takes place all around the granules and at the expense of the resorption of the BCP granules. In time, mechanical property can be observed due to the presence of the newly formed bone. Moreover, the 3-dimensional structure of the network favours recruitment, cellular differentiation, angiogenesis and the formation of bone tissue [22]. Preclinical studies carried out on mixtures of MBCP and hydrogel showed their biocompatibility, bioactivity, and resorption/osseous substitution mimicking human bone remodelling. The MBCP Gel® was developed as a putty form and is conditioned in ready-to-use syringes that facilitate the filling of bone defects, decrease the septic risk related to the handling, and ensure the homogeneity of the biomaterial. This biomaterial was the subject of a pilot study about cavity filling after dental avulsion with no infectious risk or lack of safety of MBCP Gel® being reported [23]. It was thus interesting to assess the relevance of using the same concept, largely used in dental and maxillofacial applications, in orthopaedics and to particularly evaluate period and ability of bone formation through the biomaterial.

The present clinical studies were realized to confirm the safe use and the performance of MBCP Gel®, a non-self-hardening injectable bioceramic for bone regeneration in the orthopaedic field.

2. Patients and methods

2.1. MBCP Gel® characterization

Full characterization of the MBCP bioceramic granules have been previously realized using X-ray diffraction (XRD), Fourier Transformed Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) for microstructure and granules size measurements [24,25]. After combination with the hydrogel carrier, the 3D structure was evaluated using micro CT (Skysscan 1072) analysis in order to determine the representative density of the macroporosity with intergranular spaces. Implants were sterilized by steam and ready to use.

2.2. Patients’ implantation, MBCP Gel® safety and performance evaluation in bone defect filling

Patients were followed up during 5 months to 1 year after surgery to evaluate:

- their pain level by the use of a psychometric response scale (Visual Analogic Scale [VAS]: 0 for no pain to 10 for unbearable pain) [26];
- their functional recovery, specifically the resumption of walking, or with Merle d’Aubigné’s questionnaire [27];
- any adverse events related to the MBCP Gel®;
- overall healing progress rated by X rays and/or CT-scan.

Two different studies involving MBCP Gel® in orthopaedics were conducted and the following cases are reported:

- the first study reported five patients in a non-comparative open prospective phase II clinical trial (Table 1). It was set up following French laws upon biomedical research and Good Clinical Practice, and French health authority (Afssaps: n° 2005/05/001) and local ethical committee authorizations (CHU Bordeaux CPP: n° 2004-04-12). It consisted in filling the tunnel created during surgical treatment of femoral head aseptic osteonecrosis. The percutaneous drilling was realized

<table>
<thead>
<tr>
<th>Case</th>
<th>Follow up (year)</th>
<th>Age</th>
<th>Gender</th>
<th>BMI (kg/m²)</th>
<th>Habits</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>1 year (2007)</td>
<td>44</td>
<td>M</td>
<td>24.8</td>
<td>N</td>
</tr>
<tr>
<td>P2</td>
<td>1 year (2007)</td>
<td>33</td>
<td>M</td>
<td>24.4</td>
<td>Y</td>
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<tr>
<td>P3</td>
<td>1 year (2007)</td>
<td>50</td>
<td>M</td>
<td>24.5</td>
<td>N</td>
</tr>
<tr>
<td>P4</td>
<td>1 year (2007)</td>
<td>33</td>
<td>F</td>
<td>32.0</td>
<td>Y</td>
</tr>
<tr>
<td>P5</td>
<td>1 year (2009)</td>
<td>49</td>
<td>F</td>
<td>21.8</td>
<td>N</td>
</tr>
<tr>
<td>P6</td>
<td>1 year (2006)</td>
<td>20</td>
<td>M</td>
<td>20</td>
<td>N</td>
</tr>
<tr>
<td>P7</td>
<td>5 months (2011)</td>
<td>24</td>
<td>M</td>
<td>27.8</td>
<td>Y</td>
</tr>
</tbody>
</table>

T: tobacco; A: alcohol; Y: yes; N: none.

Table 1: Patients’ description.
in young patients with the aim of performing a preservative treatment, as those patients are reported with a widened polar necrosis. An opening of 8 mm in diameter of the cortical thigh-bone was realized. Then the drilling was continued according to the axis of the collar until the greater trochanter and the cephalic necrosis without reaching the cartilaginous shell of the head (Fig. 1). The defect was filled a retro from the depth to the external cortical with approximately 3 cm$^3$ of MBCP gel. Performance in osseous repair on the necrotic zone was not expected since it wasn’t aimed.

The success of surgical procedure was principally judged by the patient’s tolerance, including infection and locoregional response to inflammation, septic complication or any adverse event related to abnormal wound healing. All patients underwent clinical and radiological follow-ups at 3, 6 and 12 months after surgery. For patients 1 to 3, the bone regeneration was as well assessed by CT scans performed one day and one year after surgery. Four grades of bone regeneration were concluded depending on the volume of the filled defect; grade 1 describes a bone regeneration of 0–25%, grade 2 (25–50%), grade 3 (50–75%), and grade 4 (75% to total repair);

- the second study concerned two types of revision surgery. The first one was the filling of a cystic long bone defect in a prospective clinical study (Afssaps: 2002/01/001/C1; CHU Fort-de-France CPP: n° 01/2001). This patient (P6) had undergone a first surgery for a cyst of the fibula with classical puncture of the lesion, but pain remained and no healing was achieved during 3 years. A first revision was made with iliac bone crest grafting. After another 3 years, no consolidation was observed and pain remained. The second revision consisted by filling the bone defect with approximately 20 cm$^3$ of MBCP Gel®. Clinical and radiological follow up at 6 months and 1 year were realized.

Patient P7 had a total hip arthroplasty at 16 years of age due to a slipped capital femoral epiphysis. After 8 years, a revision was required due to loosening and sinking of the femoral stem resulting in a leg length discrepancy of 3.5 cm. The unipolar revision was performed with cementless hydroxyapatite-coated distal cross-locking screws (Strycker) and all the spaces between metaphyseal bone host and the femoral stem were filled with one bottle of MBCP (60/40) granules of 1–2 mm diameter and five syringes of MBCP Gel®. XRD and clinical follow up was performed 5 months after surgery.

3. Results

3.1. MBCP Gel® characterization

The MBCP Gel® (Biomatlante SA, Vigneux-de-Bretagne, France) is a mixture of MBCP granules and hydrosoluble polymer as a granule carrier: BCP granules content is a mixture of hydroxyapatite (60%) and β-TCP (40%). Granule sizes varied between 80 to 200 μm, with a mean size of 120 μm in diameter (Fig. 2). SEM indicated microporosity of 25% ± 8 with micropores of less than 10 μm in diameter. As evaluated by micro
CT, the BCP granules are regularly distributed in the space, the aqueous polymer acting as an agent to maintain spaces between the granules that are required for fast biological fluid diffusion and cell and tissue colonization (Fig. 3) [19,20]. The density was measured at 49% ± 2. The material can easily be injected directly from the syringe (Fig. 4).

3.2. Patients’ characteristics

Seven patients (P1 to P7) were recruited in four different French orthopaedics departments (Cannes, Bordeaux, Fort-de-France, and Pointe-à-Pitre). Five of them were men (71%) (Table 1). They were between 18 and 50-years-old (mean average age: 36 ± 12 years), and with a BMI between 20 and 32 kg/m² (mean average of 24.6 ± 4.1 kg/m²). Patient 2 had heavy smoking habits (> 20 cigarettes/day) and consumed alcohol on a regular basis, patient 4 was obese (BMI > 30 kg/m²) and patient 7 was reported for regular cannabis use. These parameters are all known for impairing bone healing process.

Patients P1 to P5 were diagnosed and treated for femoral osteonecrosis with positive radiography and no subchondral fracture as a crescent sign, as reported as level II on the Association Research Circulation Osseous (ARCO) scale (1993). Patient 6 was seen for cystic cavity filling and patient 7 for revision of femoral stem prosthesis.

3.3. Clinical evaluation

No complication like extrusion of MBCP Gel® from the osseous defect, septic complication, abnormal wound healing, adverse event related to the MBCP Gel® were reported during the 5 to 12 months follow up of the seven patients in the four centres.

Patients P1, P2 and P3 pain perception globally decreased over time but was patient-dependant (Fig. 5).

Merle’s quotation evolved from bad or mediocre at baseline to good or excellent at 12 months after surgery (Fig. 6).

After 6 months, patient P6 no longer used crutches, and pain was no longer reported. At 1 year of follow up, no clinical complication was reported.
Patient P7 indicated no pain after 5 months (particularly no thigh pain) and no sign of instability of the stem could have been observed. He walked without limping.

3.4. Radiological results (2D analysis)

At three first months after surgery, none of the patients P1, P2, P3, P4 and P5 presented a radiolucent area of the filling site on the radiographs, showing good osseous integration of the biomaterial (Table 2A). Two patients showed partial radio opaque areas indicating bone remodelling. It is concomitant with trabecular bone ingrowth at the expense of MBCP Gel® and a new cortical zone in the lower part of the filling appeared clearly after one year (Fig. 7). This area remained opaque at 1 year only for P2, revealing a delay in bone reconstruction (Table 2A).

The defect cavity seemed totally filled in all patients just after surgery, and remained so until 12 months, except for P3 whose radiographs indicated decreasing filling 3 to 6 months after surgery, but total filling at 12 months postoperatively. The filling level was partial for all of them (at least grade 3), but became total (grade 4) for two of them (P2, P3) at 12 months (Table 2B).

For patient P6’s large cyst filling (Fig. 8A), no washing out of the defect was observed after surgery, although the gel is not self-hardening (Fig. 8B). The cavity was closed by the cortical window and 6 months later, a limited displacement appeared, however, no extrusion of the MBCP Gel® was observed. After 6 months, newly formed bone appeared clearly in the filled cystic cavity, at the expense of the biomaterial, and also between the slight displace flap and the host bone (Fig. 8C).

For patient P7 at 5 months, there was no migration of the femoral stem and good opacity of the bone substitute around the proximal part of the stem without extrusion of the MBCP Gel® (Fig. 9).

3.5. CT scan results (3D analysis)

For all patients, the mean density increased by 3 between surgery and 12 months. The filling volume of bone increased from grade 1 (0–25%) the day after surgery to grade 2 (25–50%) to grade 4 (75–100%) at 12 months. Calcifications were observed in two patients.

Table 2A
Radiological analyses revealing bone remodelling (radio opaque areas) and lack of biomaterial osseous integration (radio lucent areas).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Radio opaque areas</th>
<th>Radio lucent areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High M3 M5-6 M12</td>
<td>Low M3 M5-6 M12</td>
</tr>
<tr>
<td>P1</td>
<td>N N Yp N</td>
<td>N N Yc N</td>
</tr>
<tr>
<td>P2</td>
<td>N N Yp Yc</td>
<td>N N Yp Yc</td>
</tr>
<tr>
<td>P3</td>
<td>N N N</td>
<td>N N N</td>
</tr>
<tr>
<td>P4</td>
<td>– – –</td>
<td>– – –</td>
</tr>
<tr>
<td>P5</td>
<td>– – –</td>
<td>– – –</td>
</tr>
<tr>
<td>P6</td>
<td>N – Y</td>
<td>– – Y</td>
</tr>
<tr>
<td>P7</td>
<td>N – Yp</td>
<td>– – Yp</td>
</tr>
<tr>
<td></td>
<td>High M3 M6 M12</td>
<td>Low M3 M5-6 M12</td>
</tr>
<tr>
<td>P1</td>
<td>N N N</td>
<td>N N Yp N</td>
</tr>
<tr>
<td>P2</td>
<td>N N N Y</td>
<td>N N – Yc</td>
</tr>
<tr>
<td>P3</td>
<td>N N N</td>
<td>N N N</td>
</tr>
<tr>
<td>P4</td>
<td>– – –</td>
<td>– – –</td>
</tr>
<tr>
<td>P5</td>
<td>– – –</td>
<td>– – –</td>
</tr>
<tr>
<td>P6</td>
<td>N – N</td>
<td>N – N</td>
</tr>
<tr>
<td>P7</td>
<td>N – N</td>
<td>N – N</td>
</tr>
</tbody>
</table>

Time after surgery: D1: 24 h; M3, M6 and M12: 3, 6 and 12 months. Y: yes, N: none; p: for partial area of the filled defect, c: for complete area of the filled defect.
Table 2B
Radiological analyses revealing bone defect filling.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bone defect filling</th>
<th>Patient</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>D1  M3  M5-6  M12</td>
<td>D1  M3  M5-6  M12</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>Yc  Yc  Yc  Yp</td>
<td>Yc  Yc  Yc  Yp</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>Yc  Yc  Yc  Yc</td>
<td>Yc  Yc  Yc  Yc</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>Yc  Yp  Yc  Yc</td>
<td>Yc  Yp  Yc  Yc</td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>–  –  –  –</td>
<td>–  –  –  –</td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>–  –  –  –</td>
<td>–  –  –  –</td>
<td></td>
</tr>
<tr>
<td>P6</td>
<td>–  –  –  –</td>
<td>–  –  –  –</td>
<td></td>
</tr>
<tr>
<td>P7</td>
<td>–  –  –  –</td>
<td>–  –  –  –</td>
<td></td>
</tr>
</tbody>
</table>

Time after surgery: D1: 24h; M3, M6 and M12: 3, 6 and 12 months. High for high density areas and low for low density areas. Y: yes, N: none; p: for partial area of the filled defect, c: for complete area of the filled defect.

For patients P1, P2 and P3, a radio opaque area revealing bone remodelling was present at 12 months for two of those patients. The radio opaque areas are related to the bone remodelling and the higher density of bone trabecular integrating residual granules of MBCP Gel® into this area. Radiolucent area that would have indicated a lack of biomaterial osseous integration was never observed in any of the seven patients. Post-surgery CT scan indicated the partial filling of the created femoral defect (Fig. 10A). Twelve months after surgery (Fig. 10B), the total surface of the bone defect was completely filled by the residual granules and MBCP gel and newly formed bone. These data are consistent with results obtained with 2D radiological results in terms of biomaterial integration, consolidation and bone ingrowth.
Today, calcium phosphate bone substitutes are available and efficient for bone filling and reconstruction, but efficiently injectable calcium phosphate remains a challenge for minimal invasive surgery (MIS).

Various options are available to apply injectable and/or mouldable bone substitutes:

- first, hydraulic cements (ionic) which harden in vivo after injection. They require an extemporaneous preparation just before the injection. Ionic cements arise directly from the chemistry of calcium phosphates. However, the biological disadvantages of ionic cements are related to the absence of macroporosity, resulting in a delay of cellular colonization;
- second, organic-inorganic composites containing biological polymer such as suspension of hydroxyapatite and collagen [6] or derivates containing fibrin which allow an in situ reticulation [28]. The disadvantage of such products is the animal or human origin of at least one component;
- third, calcium phosphate ceramics in suspension in a vehicle phase which can be proposed ready-to-use. We have developed this concept of artificial bone (non-hardening injectable ceramic named MBCP Gel®; CNRS patent) [21] based on specific chemical properties and a micro- and macroporous structure for an in-depth cellular colonization and a bone ingrowth at the expense of the bioceramic.

The rheological properties of the MBCP Gel® were adapted for extrusion from a 14 gauge needle, if needed for MIS. However, surgeons reported difficulties to extrude all the injectable bioceramic from the syringe due to its high viscosity. The viscosity was defined to be sufficient to prevent extrusion by blood pressure after the defect filling. The radio opacity was limited but enough to determine over filling or extrusion into peripheral soft tissue. The seventh patient’s case demonstrated that MBCP Gel® is a good solution for perfect merge between the implant covered by hydroxyapatite and the host bone. This secondary stability
is mandatory to avoid any condensation around the screw that could result in thigh pain and sometimes breakage of the screw while aging. The easy use of the MBCP Gel® compared to the granules was demonstrated here when filling the space between the bone host and the implant, maintaining the biomaterial in the defect and in the lower extremity of the metaphyseal femur.

For the five patients with osteonecrosis, the drilling was obtained to decrease the pressure into the spongy bone of the femoral head that came along with angiogenesis followed by neo-vascularization as secondary effects. To support these preferable events, we did not fill the defect in the necrotic area. Instead only the cortical and spongious bone were filled to obtain bone regeneration. It is possible that filling the drilling defect can drive osseous proliferation and favours angiogenesis which are benefits for bone reconstruction in case of necrosis. The concerned patients reported an overall decrease of their pain perception which were still patient-dependant. The difference already appeared before implantation, since one patient had no pain and remained so over time while two others were in pain before surgery.

On the contrary, the safety of use was clearly demonstrated for all seven patients since no adverse event had been reported.

From the clinical point of view, improvement and functional recovery were demonstrated for all seven patients with pain reduction (no residual pain during 6 months follow up) and consolidation or Merle’s quotation increase at 12 months after surgery.

This was confirmed by X-ray and CT scan analysis, with CT-scans giving additional quantitative information in terms of bone ingrowth. Globally, the radiographs and CT scans revealed trabecular bone ingrowth at the expense of the MBCP Gel®, and a new cortical zone on the lower part of the filling after one year delay. Moreover, the defect cavity seemed totally filled for all patients just after surgery or at least at 12 months postoperatively. Thus, in addition to the safety demonstrated in these orthopaedics cases, the study revealed the performance in terms of resorption and bone ingrowth at the expense of the injectable bone void filler. The bone regeneration with healthy bone architecture, as seen for patient 6, allowed a resumption of normal activities, since arm crutches were no longer needed.

In hip revision surgery for stem prosthetic replacement, MBCP Gel® was a useful bone void filler at all spaces between the bone and the prosthesis, allowing bone regeneration and osteointegration.

For every criterion, the heavy smoker (patient P2) showed an altered profile. BMI (P4) and cannabis consumption (P7) could have had an impact on bone reconstruction, too, but the limited number of patients and the design of the pilot study did not allow the link between impaired bone healing and these parameters.

It was demonstrated that the composite was able to preserve bone remodeling in regards to the sites of application and showed good properties in terms of resorption and bone ingrowth at the expense of the injectable bone void filler.

The presented cases confirm the osteogenic property, safe use and the performance of non-hardening injectable calcium phosphate bioceramic in form of the MBCP Gel® in orthopaedics bone defect filling.

5. Conclusion

After maxillofacial use of MBCP Gel®, the present clinical cases in orthopaedics confirm the efficacy of bone ingrowth at the expense of a non-self-hardening injectable bioceramic. The results after one year of clinical follow up demonstrated the bone regeneration in osteoarticular bone defects in spite of critical osteonecrosis area, and the patients’ clinical improvement. The present cases therefore confirm the osteogenic property, the safety of use and the performance of non-hardening injectable calcium phosphate bioceramic in orthopaedics applications.

Disclosure of interest

G.D.: Biomatlante SA share older, inventor of the MBCP gel. M.D.: occasional clinical advisor for Biomatlante SA. T.F., F.V., A.P.U. and J.L.R. declare that they have no conflicts of interest concerning this article.

Acknowledgments

To Dr Pelé (CHU de Bordeaux) for his help in CT scan analyses.

References