Lack of union within 6 to 8 months of a primary treatment is generally considered pseudarthrosis.\(^1,2\) The diagnosis of pseudarthrosis in diaphyseal fractures of long bones requires a period of at least six months.\(^1\) However, delayed fracture healing results in long-term persistence of disability, which affects the quality of life of a patient more adversely than ischemic heart disease and renal disease requiring dialysis.\(^1,2\)

Approximately 2.5% of long bone fractures develop into pseudarthrosis.\(^1,4\) The risk for developing pseudarthrosis is higher, particularly in severe open fractures, transverse fractures, soft tissue interposition or inefficient fixation.\(^3,4\) Nonunion is associated with many factors including mechanical and biological environments.\(^2,5-7\) A poor mechanical environment refers to a poor stability of the fracture site, which allows overactivity at the fracture tip. A poor biological environment refers to an impaired blood supply to the fracture tip, infection or inadequate soft tissue coverage.\(^3,4\)

There is no single treatment for pseudarthrosis. As basic principles of fracture treatment also apply for nonunion treatment, possible fixation techniques are
similar to those used for treatment of acute fractures.\textsuperscript{[1,3]} Many internal and external techniques have been described for nonunion.\textsuperscript{[1,3]} Modalities often used include resection of bone fragments at the site of nonunion, internal fixation combined with allografts or autografts, intramedullary nailing, Ilizarov’s external fixation method and electrical stimulation.\textsuperscript{[1-3,7]}

Periosteal loss is common in fragmented fractures, open fractures and similar orthopedic traumas. Soft tissue injury loss during several operations and traumas also results in periosteal loss.\textsuperscript{[9,10]} The periosteum is very critical in fracture healing since it shows mechanical resistance to the fracture fragments and provides blood circulation and osteogenic progenitor cells to the underlying bone in the cortical region.\textsuperscript{[9,10]}

Hyalonect (Fidia Farmaceutici SpA, Abano Terme PD, Italy), a knitted mesh of hyaluronic acid fibers, is a bioresorbable coverage graft designed for stabilization of fracture fragments from comminuted fractures and of grafts used for bone defects and pseudarthrosis. It has also been reported to facilitate angiogenesis. The material can be fixed to surgical site by sutures or bone fixation devices.\textsuperscript{[9]}

In this study, we evaluated the results of union in patients treated with open reduction and allografting combined with Hyalonect for pseudarthrosis.

Patients and methods

The study included 11 patients (8 male, 3 female) treated with open reduction, followed by plate and nail fixation for pseudarthrosis between 2007 and 2010. Mean age was 44.6 (range: 23 to 57) years. Pathological fractures, intra-articular fractures and fractures involving children younger than 18 years of age were excluded. Preoperative medical history and physical examination of the patients were completed. Radiological and laboratory studies were reviewed.

Fractures were caused by traffic accident in 3 patients and fall in 8. The upper extremity was involved in 5 patients (5 humerus) and the lower in 6 (tibia in 4, femur in 2). All fractures underwent previous surgical treatment (one operation in 1 patient, 2 operations in 7 patients, 3 operations in 2 patients, and 6 operations in 1 patient). There were no bone defects of over 4 cm or vascular palsy. One patient had radial nerve palsy associated with prior surgery. All patients underwent osteosynthesis with plates and screws and allografting. Grafts were wrapped and stabilized with Hyalonect (5×10 cm) (Table 1).

The decision for surgical intervention was taken after the clinical and laboratory confirmation of the absence of any infection. Incisions were made appropriate to previous intervention of soft tissue coverage. All previous fixation materials, if any, were removed. All patients had evidence of nonunion from previous surgical intervention. Fracture fragment ends were sclerotic and atrophic in all cases. The soft tissues between the ends of the fracture were debrided and the bone ends were regenerating, resecting the areas of sclerosis. During regeneration, none of the cases underwent a shortening exceeding 1.5 cm. Existing shortenings were associated with prior surgical procedures. Medullary channels were cleared. Debrided and regenerated bone ends were connected and the resulting reduction was stabilized with a plate and screw fixation. A spongy granular allograft was placed between and around the bone ends and

Table 1. Summary of data for all patients.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex / age</th>
<th>Location of fracture</th>
<th>Cause of fracture</th>
<th>Initial treatment</th>
<th>Number of previous surgical treatments</th>
<th>Complication</th>
<th>Fracture classification upon first presentation AO</th>
<th>Open / closed fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M / 57</td>
<td>Left crus, lower 1/3</td>
<td>Fall</td>
<td>ORIF</td>
<td>2</td>
<td>None</td>
<td>43A3</td>
<td>Closed</td>
</tr>
<tr>
<td>2</td>
<td>F / 57</td>
<td>Left femur, lower 1/3</td>
<td>Traffic accident</td>
<td>ORIF</td>
<td>1</td>
<td>None</td>
<td>33A3</td>
<td>Closed</td>
</tr>
<tr>
<td>3</td>
<td>M / 43</td>
<td>Right humerus, intermediate 1/3</td>
<td>Fall</td>
<td>ORIF</td>
<td>2</td>
<td>None</td>
<td>12A1</td>
<td>Closed</td>
</tr>
<tr>
<td>4</td>
<td>F / 40</td>
<td>Right humerus, lower 1/3</td>
<td>Fall</td>
<td>ORIF</td>
<td>2</td>
<td>None</td>
<td>13A2</td>
<td>Closed</td>
</tr>
<tr>
<td>5</td>
<td>F / 40</td>
<td>Right humerus, intermediate 1/3</td>
<td>Fall</td>
<td>IMN</td>
<td>2</td>
<td>None</td>
<td>12A1</td>
<td>Closed</td>
</tr>
<tr>
<td>6</td>
<td>M / 35</td>
<td>Right humerus, intermediate 1/3</td>
<td>Fall</td>
<td>ORIF</td>
<td>3</td>
<td>Radial nerve lesion (prior)</td>
<td>12A2</td>
<td>Closed</td>
</tr>
<tr>
<td>7</td>
<td>M / 55</td>
<td>Left femur, lower 1/3</td>
<td>Fall</td>
<td>ORIF</td>
<td>6</td>
<td>Infection</td>
<td>33A3</td>
<td>Open</td>
</tr>
<tr>
<td>8</td>
<td>M / 56</td>
<td>Right crus, lower 1/3</td>
<td>Fall</td>
<td>ORIF</td>
<td>2</td>
<td>None</td>
<td>43A3</td>
<td>Closed</td>
</tr>
<tr>
<td>9</td>
<td>M / 40</td>
<td>Right crus, lower 1/3</td>
<td>Traffic accident</td>
<td>Ext. Fix.</td>
<td>2</td>
<td>None</td>
<td>43A3</td>
<td>Open</td>
</tr>
<tr>
<td>10</td>
<td>M / 45</td>
<td>Left humerus, intermediate 1/3</td>
<td>Fall</td>
<td>ORIF</td>
<td>2</td>
<td>None</td>
<td>12A2</td>
<td>Closed</td>
</tr>
<tr>
<td>11</td>
<td>M / 23</td>
<td>Right crus, lower 1/3</td>
<td>Traffic accident</td>
<td>Ext. Fix.</td>
<td>3</td>
<td>None</td>
<td>43A3</td>
<td>Open</td>
</tr>
</tbody>
</table>

Ext. Fix.: external fixation, IMN: intramedullary nailing, ORIF: open reduction + internal fixation
secured by placing an absorbable suture (Vicryl no: 0; Fidia Farmaceutici SpA, Abano Terme PD, Italy) on each end in order to facilitate manipulation (Fig. 1). This Hyalonect was wrapped around the graft and fixed with sutures (Fig. 2). In cases where more than one Hyalonect was used, attention was paid not to superimpose the meshes. Finally, the surrounding soft tissue coverage was closed according to their layers in order not to damage the Hyalonect and grafts.

**Results**

Patients were followed up weekly until the removal of sutures and monthly thereafter. Follow-up examinations included wound care, clinical examination of movement of adjacent joints and radiological examination. Clinical absence of pain and activity at the fracture site and radiographic sign of callus formation were considered improvement (Fig. 3).

Mean follow-up time was 31 (range: 12 to 48) months. All patients achieved union at a mean of 6 (range: 4 to 8) months. None of the patients developed infection, malunion or implant failure except one.

One patient maintained preexisting radial nerve lesion. Evidence of a superficial infection was found in the patient who had undergone 6 prior surgeries and the infection was reduced at Week 2 with appropriate treatment. This patient achieved union at 8th postoperative month.

No patient developed angular deformity. However, 4 patients had clinically significant shortening of a mean of 2.5 (range: 2 to 3) cm. The shortening was
quite common, particularly in cases with femoral nonunion. The fracture ends of bones in patients with humeral pseudarthrosis were regenerated. As no clinically remarkable shortening developed, it was not reported.

One of the patients with pseudarthrosis had limited joint range of motion between 0 and 20 degrees, particularly in the knee joint, associated with prior surgery. In patients with humeral fracture, elbow and shoulder range of motion was almost complete. Patients with tibial pseudarthrosis had no limited movement of the knee. However, they had a mean loss of motion of 15 (range: 5 to 30) degrees in the ankle. Mean dorsiflexion of the ankle was 8 (range: 0 to 15) degrees and the mean plantar flexion was 30 (range: 18 to 45) degrees.

Union was achieved at an average of 4 months in patients treated for humeral pseudarthrosis, 6 months in patients with femoral pseudarthrosis, and 5 months in patients with tibial pseudarthrosis.

Discussion
Treatment of nonunion poses many challenges to both patient and surgeon. Any delay in treatment may result in prolonged morbidity and delayed return to work, painkiller addiction and emotional breakdown. Therefore, appropriate treatment is critical. In the current study, all patients, with the exception of two cases, had undergone prior surgery (average: 2.5 surgeries; range: 1 to 6 surgeries). Mean work loss associated with the condition was 20.2 (range: 12 to 40) months for the previous period, which led us to consider the use of Hyalonect for fracture healing despite its high cost (TL 3,000).

An additional reason behind the choice of Hyalonect as a wrap was the possible interference of the prior trauma and surgical procedures on structural and functional maintenance of the periosteum. In such cases, regeneration of the bone tissue can be substantially influenced. The periosteal fibrous tissue is a membrane, which is composed of elastic tissue and blood vessels, and it is tightly attached to the bone, providing a mechanical resistance to fracture. It consists of osteoblasts and mesenchymal progenitor cells. It also helps supply blood to the underlying bone tissue. The grafts or graft-like materials used in the absence of the periosteum may break down and adhere to the surrounding soft tissues. If grafts are not stabilized to prevent movement, pain may occur at the fracture site. Furthermore, experimental and clinical studies have shown that a secure and stable fixation of the graft in the application area have contributed to accelerate improvement and union.
between the graft and the bone.\cite{11} Biological tissues, protein-based adhesives or synthetic membrane-like material have been used to repair this membrane. The biological and mechanical properties of these materials are far from being ideal for the required use.\cite{9}

As a surgical mesh, Hyalonect functions as a scaffold for the periosteum replacement to limit migration of the grafts and graft-like materials used in this setting. In an experimental study, it was histologically shown that Hyalonect prevented grafts from spilling out of the defective areas and provided a constrained environment for tissue healing.\cite{10} In addition, the use of Hyalonect as a barrier between the radial nerve and bone grafts may be beneficial in protecting the radial nerve from fracture callus in humeral fractures.

Histological evaluations also indicated that Hyalonect (a knitted mesh) consistently refilled the defect area with viable host cells and protected the penetration of fibrous tissue into the defect area, thus allowing the regeneration of a new functional bone marrow environment. Additionally, evidence shows that because of cell infiltration into the mesh, Hyalonect began to reshape the surrounding local environment to mimic the structure of original periosteal membrane up to Week 6.\cite{9}

Hyaluronic acid plays a major role in regulation of angiogenesis.\cite{12,13} It has been shown that in close contact with the bone tissue, it is involved in bone morphogenesis and early events of osteogenesis,\cite{11,14} and modulates the effects of a few cytokines and growth factor.\cite{11,14} In an animal study using Hyalonect, Rhodes et al. reported revascularization at days 30 and 60 following penetration of macrophages and attributed it to the chemotactic and angiogenic potential of the hyaluronic acid oligosaccharides which are produced during macrophage-mediated degradation of the HYAFF 11 fibers composing the Hyalonect.\cite{9}

Hyaluronic acid has been commonly used in various forms, including nonwoven fabrics, membranes, sponges and tubes in both clinical products, and experimental trials. Its efficacy has been demonstrated by several studies when used as a scaffold in reconstruction of skin,\cite{17,18} cartilage,\cite{17,19} bone,\cite{18,20,21} connective tissue,\cite{22,23} intervertebral disc,\cite{24} nerve pools,\cite{23} small-diameter vascular replacement material,\cite{25,26} and hepatic tissue.\cite{27}

Histological findings from applications of hyaluronic acid show that it may contribute to homeostasis of the physiological environment of the periosteum. This observation has a significant implication as previous reports have suggested that incomplete healing of the bone allografts are correlated with lack of an osteogenic or angiogenic substitute of the periosteum on the bone grafts.\cite{30}

In clinical practice, repairs of large bone defects are usually performed using osteogenic filling substances\cite{29} such as demineralized bone matrix (DBM), generally for osteoconduction, together with mineral constituents including calcium sulfate.\cite{30} The method of defect closure is a critical determinant of a successful surgical repair. Hyalonect plays a significant role in fracture healing and bone regeneration, providing bone coverage similar to the periosteum.

Hyaluronic acid shares bone induction characteristics with osteogenic substances such as calcitonin and bone morphogenic proteins. Proteins such as fibrinogen, fibrin, fibronec tin and collagen, which are necessary in bone healing, have been shown to bind to hyaluronic acid.\cite{19} In addition, bacteriostatic activity of hyaluronic acid has been reported, giving importance to the presence of hyaluronic acid in healing tissues in inhibiting bacterial contamination of the surgical wound.\cite{4} In the present study, two patients experienced short-term drainage. However, none of the patients required removal of Hyalonect. It has previously been shown that hyaluronic acid becomes completely invisible after one year of complete esterification.\cite{11}

In the current study, the most commonly involved bone was the humerus (46%), followed by the tibia (36%), femur (18%). In the literature, the humerus was the most commonly involved bone while pseudarthrosis was more common in the tibia than the femur.\cite{13,14}

Conventional treatment of pseudarthrosis includes revitalization of fracture ends, bone grafting and rigid internal or external fixation. The most common grafting technique used is autogenous spongiosa grafting, which has the most potent osteogenic factor. However, it can be derived only from a number of areas of the body. The amount of harvest from each of the four donor sites covers a defect with an average of 2 cm in length. As the number of resources available for autogenous graft is restricted during grafting, the amount of defect to be covered is also restricted. In addition, grafts undergo a volume loss of 20 to 40% following massive spongiosa grafting. We preferred allografts as the majority of our patients had undergone previous operations and some rejected bone graft harvesting. Hyalonect, a periosteum-like tissue, was chosen in order to achieve stabilization of the graft and improve the union of fracture.

Plates were used for fixation. Nwagbara\cite{1} used open reduction, plate and screw fixation and autografting for management of long bone pseudarthrosis. Nonunion was found in 17% of these cases. In the literature, rates of nonunion after treatment for pseudarthrosis range from 8% to 12%.\cite{7,12,13}
The treatment of pseudarthrosis of the humeral shaft is challenging and may require more than one surgical intervention. Success rates decrease and complication rates increase as the number of surgical procedures increase. Humeral pseudarthrosis can be managed with plate fixation, intramedullary nailing, cortical bone grafting and external fixators. The plate method is reported to be the most successful treatment option in humeral pseudarthrosis. For a satisfactory treatment, a rigid fixation is required using 6 cortical screws. On the other hand, it is important to have an efficient debridement of soft tissues and bone and obtain a good blood supply to the surrounding soft tissue. A good contact should be established at fracture ends for healing.

Celebi et al. used open reduction, plate fixation and autogenous bone grafting for treatment of pseudarthrosis in 24 patients. Union was achieved after a mean of 19 weeks. Oztürkmen et al. achieved union in 94% of patients treated with plate-screw fixation and autogenous grafting.

Rubel et al. achieved union in 92% of patients with humeral pseudarthrosis treated with open reduction and internal fixation. An additional 3.5 mm-thick plate was used in cases with a microactivity in the area of pseudarthrosis. A second plate due to presence of microactivity following the use of the first plate was necessary in 66% of patients. In addition, they showed that the two-plate construct biomechanically provided a more stable fixation and prevented microactivity in the area of pseudarthrosis. We also preferred to use two plates in one case due to lack of stability.

Furthermore, rehabilitation can be initiated immediately after plate fixation. There is no need to restrict joint mobility. Our patients maintained their existing joint mobility.

Intramedullary nailing can also be used for fixation. With the Seidel intramedullary humeral nail, 58 patients (34%) failed to achieve union and required a second intervention due to poor distal rotational stability. Antegrade nailing may be associated with shoulder dysfunction. Retrograde nailing may result in loss of elbow movements, valgus-varus malunion, crack propagation at the insertion site, fracture or avulsion, or radial nerve paralysis. Other disadvantages of intramedullary nailing include impaired endosteal circulation, spread of infection to other humeral sites, occlusion of the medullary channel, difficulty in use in the presence of deformity and the requirement of a second surgical procedure for removal.

The Ilizarov method is another fixation technique used for treatment of pseudarthrosis. Atalar et al. evaluated the outcomes of patients treated with an external fixator (unilateral or circular) vs. plate fixation for treatment of humeral pseudarthrosis. The authors found a statistically significant difference in union time and DASH scores among the three groups and concluded that the surgeon’s experience is important in selecting the surgical procedure to be performed. Similarly, problems have been reported with the use of the Ilizarov method in the treatment of humeral pseudarthrosis, including incompatibility of the device, nail bed infection, nerve injuries and septic arthritis. Fracture may recur following fixator removal. Furthermore, the surgeon must be thoroughly familiar with the system.

Oztürkmen et al. achieved union in 92% of 46 patients treated with the Ilizarov method for pseudarthrosis. The fixator remained in the body for a mean of 208 days. Pin tract infection developed in 28 patients, sympathetic dystrophy in 3, and fracture recurred following device removal in 3 patients. A quarter of the patients treated with segment transport required re-grafting due to delayed union. Three patients had angulation after fracture union.

An additional problem associated with external fixators is incompatibility of the body with an external device. Social and psychological interactions may also result in complications. Furthermore, as in our cases, patients treated with external fixator for therapeutic purposes may develop pseudarthrosis which may decrease their patience.

Limited range of motion is common in patients with pseudarthrosis following prior surgery or conservative treatment. This complication is often seen particularly in femoral, diaphyseal and supracondylar fractures. When pseudarthrosis is combined with limited range of motion, treatment becomes more challenging and the patient may experience functional problems. These two conditions can be treated simultaneously or individually. In the presence of limited range of motion, we preferred to manage the pseudarthrosis first by initiating joint movements in order to maintain the existing range of motion and prevent further restriction in the range of motion due to plate fixation. All of our patients maintained their existing range of motion.

In conclusion, Hyalonect is a suitable material for reconstruction of integrity in pseudarthrosis, which may lead to severe problems if not treated well, and that orthopedic reconstruction which requires maintenance of the relative position of the sutured bone tissue (such as
autografts, allografts and bone graft substitutes) and bone graft fragments from comminuted fractures may benefit from this novel biodegradable mesh. However, further clinical trials including control groups are necessary.

**Conflicts of Interest:** No conflicts declared.

**References**


