Injury, Int. J. Care Injured (2007) 38S, S11-S18

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INJURY
INTERNATIONAL JOURNAL OF THE CARE OF THE INJURED

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Risk factors contributing to fracture non-unions

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KEYWORDS Non-union; Pseudoarthrosis; Delayed union; General Risk factors in fracture healing; Local Risk factors in fracture healing; Trauma mechanism; Osteogenetic disorders; Orthometer; Strain-gauge bar; Estensimetry

Introduction

Many studies have been carried out on the matter of pseudoarthrosis since the 1920s, where pseudoarthrosis is defined to occur when consolidation cannot be completed without new biological or mechanical stimulation. Since then, several authors have contributed their knowledge of osteogenetic mechanisms, placing the emphasis on the risk factors of a non-union. In general terms the risk factors contributing to non-union can be separated into general and local factors (Table 1). The purpose of this study is to identify and report on the different factors which have been implicated in the pathogenesis of non-union of fractures.

Table 1
Risk factors contributing to non-union

General risk factors	Local risk factors
Gender	Fracture personality
Age	Type of fracture
Diet	Exposure
Diabetes	Infection
Osteoporosis	Multiple
Muscular mass	trauma/fracture
Smoking	
Alcohol NSAIDS	

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General risk factors

Delayed fracture consolidation can be due to factors related to the magnitude of trauma and the subsequent treatment interventions. Age, sex, mechanism of injury and type of fracture, associated injuries, comorbidities, lifestyle and pharmacological agents are all factors that could interfere with the fracture healing response. Different types of pseudoarthrosis exist and reflect different pathways of developing this complication. Atrophic non-unions are associated with factors acting directly on the early phases of fracture healing,[1] while hypertrophic nonunions relate mostly with factors acting on the "reorganisation" phase of bone healing.[2]

Gender

Different incidence in fracture union between men and women is found in patients over the age of 55 years, with a higher percentage for the female sex. After the menopause, women have a lower rate of oestrogen, that plays an important role in promoting bone formation, stimulating anabolic and reducing catabolic processes.[3] A delayed formation of bone matrix can be found in these patients. Four weeks after the fracture episode the newly formed bony callus still appears to be made of a thin layer of trabecular bone and cartilage. There is, therefore, an insufficient formation of bone matrix which eventually causes instability between the two fracture fragments.[4]

Age

Children's periosteum is rich in osteoblasts and in vascularisation.[5] For this reason, children and young adults form new bone rapidly and the vast majority of their fractures unite. The newly formed bone follows the process of remodelling which restores the original anatomy. Given the considerable speed of bone healing in children, it is vital to intervene early and close to the fracture event.[6] In adults the periosteum is partly fibrous and this is why the production phase of the bone callus is slower. However, the reorganisation of the newly-formed bone augments mechanical stability until fracture union is obtained.[5]

Diet

During the fracture healing process, there is an increase in metabolism requirements. For this reason, the importance of diet rich in protein, calcium and phosphorus, and Vitamin D has been assessed in a number of clinical trials.[7] Nutritional deficiencies seem to have the maximum influence on the later phases of bone callus formation; at the initial phases, in fact, there is an increase of the metabolic requirements and deposited calcium is utilised.[7]

A lack of nutritional contribution does not cause a significant delay in fracture union. Mostly it affects the mechanical strength of the bony callus itself, and thus requires a longer period of protection, until mineralisation is completed.[8]

Diabetes

Diabetes is often associated with delayed fracture union. There are several implicated factors; mainly vascular and neuropathy problems. A clear reduction in the formation of collagen in the bone callus and a marked reduction of cells involved at the repair process[9] have been noted in diabetic patients. Patients with a well regulated diabetes under insulin therapy have a reduced risk.[10]

Osteoporosis

Patients with osteoporosis experience a progressive loss of bone mass and an increase in the risk of fractures.Osteoporotic bone lacks the capacity to regenerate and regain valid biomechanical characteristics. It is a bone that has an altered structure due to the reduced presence of trabecular components, which causes the loss of mechanical resistance. There is a reduction of osteoblasts and thus to callus production.[11]

Osteoporosis therapy must be provided from the early phases of fracture repair. Recently, the effect on bone healing of the anti-osteoporosis agents biphosphonates has been compared to that of theriparatide. Biphosphonates have an anti-catabolic activity, while theriparatide acts by stimulating the osteoblasts.[12] Reduction and application of internal or external fixators that allow early mobilisation of the affected limb are essential in osteoporotic patients. On the contrary prolonged immobilisation of the limb weakens the bone. Post-trauma osteoporosis, or Sudek's disease, may also occur in young patients, when the fractured limb is kept immobilised or deprived of physical stimulation for too long.[13]

Muscular mass

The evaluation of the muscular mass of the affected limb is also important. Muscular atrophy present prior to the trauma may be a factor that negatively influences bone healing. In the late stages of bone callus formation and during re-organization of newly-formed tissues, mechanical stimuli that act on the bone are very influential. Good muscle tone allows a more rapid functional recovery allowing better biomechanical stability of the fracture.[14]

Smoking

It has been statistically proven that smoking increases the risk of delayed fracture union and of pseudoarthrosis.[15] Nicotine prevents cellular proliferation during the fracture healing process, altering the maturing of macrophages and fibroblasts and acting directly on osteoblasts. It is also a vasoconstrictor agent, causing an alteration of the tissue perfusion with consequent hypoxia and ischemia. A deficit in the formation of haematomas at the fracture site and an alteration of biomechanical properties in the newly-formed bone has been assessed in patients who smoke more than 10 cigarettes per day.[16] Decreased vascularisation of a fracture site has been proven to cause delayed bone healing leading to atrophic pseudoarthrosis.[17]

Alcohol

Ethanol plays a key role in inhibiting healing, especially when it is taken in excessive doses in the post-trauma period.[18] Alcohol abuse in patients with fractures inhibits new bone formation, therefore seems to be associated with an increased incidence of delayed unions. The

newly-formed bone is lacking of mineralisation and consequently has decreased mechanical stability at the fracture site due to low rigidity of the newly-formed bone.[19]

NSAIDs

Pharmacological therapy with NSAIDs causes a side effect of delayed fracture union, especially when they are administered for a period longer than 4 weeks or when they are used immediately after the surgical operation as painkillers.[20,21] In fact, they play a role in the reduction of osteoblastic activity. They also inhibit the synthesis of prostaglandins, which in turn causes a delay in the formation of bone callus. Studies carried out on the administration of high doses of Indometacin show an inhibition of macrophage activity, acting on interleukin-1 (IL-1).[22]

Local risk factors

Local factors that can aid the evolution of pseudoarthrosis are linked to the trauma mechanism, to the type of fracture produced and to any associated injuries.[5] These factors are considered to be essential and careful evaluation of them can help to plan successfully the treatment interventions in order to avoid the development of non-unions.

Fracture personality

This includes the mechanism of injury i.e. a high or low energy trauma, vascular damage, the site of the affected bone (diaphysis, metaphysis, epiphysis), the comminution of the bone and the inter-fragmentary gap and displacement.

Low energy trauma

These generally cause fewer injuries to the soft tissues, and to the bone, thus is considered to represent a more "benign" injury. The relatively minimal fracture site haematoma, the more stable fracture configuration and the minimal damage to the soft tissues, to the periosteum rarely leads to healing delays and complications.

High energy trauma

This causes more complex, more comminuted and displaced fractures,often with considerable tissue loss, serious damage to the soft tissues and to the vascular system. All these factors may lead to a reduction of blood flow to the fracture site, and decrease the physiological inversion of the endosteal flow.

Experimental studies have shown a reduction of the cortical blood flow up to 50% immediately after trauma due to vasoconstriction in the marrow and periosteum vessels. When the repair process begins, intra and extra bone arterial circulation increases, with a peak of vascularisation of the bone callus about 2 weeks later. At the same time, the marrow circulation decreases considerably and thus a transitory inversion of the endosteal circulation takes place that changes from a centripetal force to a centrifugal force. This becomes apparent in the increase in cortical flow, generated by the swelling of the periosteum, of the muscles and of the surrounding soft tissues, that guarantees a contribution of osteogenetic molecules to the fracture site.[23]

Large lesions of the soft tissues and large haematomas have a negative influence on this physiological process, causing a reduction in cortical flow that appears to be the only action that can guarantee sufficient bone vascularisation in the first two weeks after the trauma. The reduced supply of nutrients and osteogenetic cells at the fracture site increases the risk of bone necrosis and leads to inhibition of the repair process. All this may lead progressively to the development of a non vital (atrophic) pseudoarthrosis.[24]

Fractures caused by high energy trauma are also more difficult to reduce and stabilise, with more problems linked to the choice of the most effective osteo-synthesis and its correct application.

Vascular damage

Fractures are generally associated with various degrees of vascular damage. In those cases where the bony fragments are devascularised or where periosteal stripping and destruction produces necrotic bony fragments and large defects the risk of an atrophic non-vital pseudoarthrosis is high It has been shown that serious damage to one or more important veins in the lower limb increases the incidence of pseudoarthrosis by about threefold.[25]

Topography

Fractures of the metaphysis have a lower incidence of union defects and shorter healing times compared to fractures of the diaphysis. This is due to the fact that the healing process of

diaphyseal fractures starts from the periosteum and endosteum, while the cortical bone must be reabsorbed before the fragments can consolidate. This means that the endosteal vascularisation and the periosteum must be damaged as little as possible for the fracture to be able to consolidate. On the contrary, the repair mechanism of metaphyseal fractures, starts from cancellous bone that regenerates more rapidly and also has greater vascularisation. Healing processes in the metaphyseal area are therefore faster and less susceptible to obstructive factors than those encountered by diaphyseal fractures. Ossification can occur even when there is considerable damage to the periosteum and to the vascularity of the fracture fragments.[26]

The anatomical site of the fracture compared to the location of the vessels that supply the bone is also important. Fractures that are distal to the nutritional centre have a greater risk of association with impaired blood supply and therefore a greater risk to develop an atrophic pseudoarthrosis.[5]

Inter-fragmentary gap

The presence of an inter-fragmentary gap is closely associated to the onset of pseudoarthrosis. It has been shown that, when internal fixators are used, inter-fragmentary gaps larger than 2 cm may be a cause of pseudoarthrosis.[27]

Type of fracture

According to the AO Classification by Muller (1984)[28] we can identify four different groups of fractures with the greater or lesser tendency of evolving towards various types of pseudoarthrosis.

Simple (stable)

Simple fractures - types A2 (oblique), A3 (transverse) and B2 (with a angulated wedge) - have a single site or a wedge, potentially stable, that has a sufficient support to allow inter-fragmentary compression. These fractures are characterised by the presence of small haematomas that provide a minor biological contribution to healing. They can sometimes also be associated with vascular or soft tissue damage that causes further problems. If the healing process is affected then in most of the cases it evolves to an oligotrophic pseudoarthrosis.

Complex (unstable)

Complex fractures - types A1 (spiral), B1 (spiral wedge) and B3 (multi-fragmentary wedge) - are potentially unstable, as they do not have a sufficient support area to guarantee fixation by simple inter-fragmentary compression. Fractures of this type tend to evolve into hypertrophic pseudoarthrosis as the vascularisation of the fracture site is not seriously damaged and the fracture haematoma supplies a suitable biological contribution, but often have excessive mobility between the fragments which delays union and consolidation.[29]

Comminuted (highly unstable)

In comminuted fractures - types C1 (spiral complex) and C3 (multiple fragments) - the multiple fragments and comminution represent a high risk of devascularisation and necrosis of the fragments, with a consequent loss of substance and the need to provide a biological stimulus, in addition to mechanical stimulus to obtain a good level of healing. The comminution of a fracture causes doubling of the risk of pseudoarthrosis. This is due to the fact that the devascularised and necrotic fragments are a physical impediment to the normal development of an endosteal callus that is not always substituted adequately by periosteal ossification.[30]

Comminuted fractures also created large problems for stabilisation, as it is not always possible to obtain stable synthesis that will facilitate callus formation and maturation. Considering these elements, the evolution of these fractures in the event of failure mainly leads to oligo/atrophic pseudoarthrosis.[31]

Segmental (potentially unstable)

Only type C2 (two segments) belong to this group, which have a dual fracture site on the same bone segment. This causes greater difficulties for suitable stabilisation as the two sites can have different characteristics and different fixation needs.

In a large number of cases, due to problems mainly linked to circulation problems, it is possible to obtain good level of healing of one of the two fracture sites, while the other one evolves towards pseudoarthrosis.[28] This group, which is actually extremely heterogeneous, will evolve towards a type of pseudoarthrosis that differs depending on the type that each fracture site in the segment involved belongs to. Finally, type C fractures are

the ones that have the greatest tendency to evolve into pseudoarthrosis: literature show about 40% of type C fractures of the diaphysis of the femur evolve towards pseudoarthrosis, while type B and A have much lower percentages of incidence: 15% and 6% respectively.[32]

Exposure

Exposure of the fracture is another factor which can cause a fracture to develop into pseudoarthrosis with consequent risks to contamination. The first unfavourable element caused by exposure is external evacuation of the fracture haematoma, that causes the almost total depletion of osteo-competent elements (mediators, cytokines, osteoblasts, platelets) that are needed for repair.

Also, in exposed fractures, there can easily be a loss of vascular connection between muscles, periosteum and bone with the formation of a large amount of fibrous tissue, which is biologically inactive, that prevents the newly formed vessels and osteoblasts cells to reach the fracture site, and therefore stimulate repair.[33]

The Gustilo-Anderson classification carried out in 1976 divides exposed fractures into three groups that do not have a direct correlation with the evolution into pseudoarthrosis.[34] However, literature shows that grade 2 and 3 open fractures have a greater predisposition to pseudoarthrosis, as they are related to high energy trauma with considerable necrosis of the soft parts.[35] Severe fragmentations of the bone together with damage to the periosteal circulation reduces further the availability of osteogenetic factors at the fracture site and increases significantly the rates of necrosis and atrophic nonunion.

There is sometimes greater damage in closed fractures, especially in the lower limbs than open ones. Compartment syndrome can also develop that contributes considerably to the biological damage. The intra-compartmental pressure increase is in fact associated with a decrease in the blood flow to soft tissues that also influences the flow of osteo-competent substances at the fracture site.

There is also a correlation between a delay in fasciotomy and the healing time for a fracture that is extended to 20 weeks after a wait of more than 24 hours.[36] Therefore the degree to which the soft tissues and the periosteal vascularisation are affected can be more decisive than the exposure of the fracture site itself.

Exposed fractures also bring about problems in the choice of technique used to stabilise them, as it is necessary to take into account the state of the surrounding and overlying soft tissues.

In the event of severe extent of exposure, with considerable loss of bone substance and soft tissue, the choice must be between either an attempt to save the limb by osteosynthesis or proceeding to amputation. The Mangled Extremity Severity Score (MESS, 1990) analyses the various parameters regarding local injury and the patient's general state assisting the surgeon in the decision making process (ref). A mangled extremity severity score (MESS) <3 is an good prognostic indicator - which justifies all the efforts to save the injured limb.

For values between 3 and 7, the prognosis is uncertain: these are the most controversial cases in which the negative evolution of a fracture into a persistent kind of pseudoarthrosis is more common. For a MESS >7, prognosis is always negative. These are cases in which amputation, represents actually an improvement in the *quoad vitam* and *quoad valetudinem*[37] prognosis.

Infection

Infection is not a synonym of pseudoarthrosis, however it may contribute to the creation of conditions, such as sequestrum (necrotic cortical bone due to pus), osteolysis (generated by infected granulation tissue), interposition of necrotic soft tissue between the fracture fragments and to hardware loosening and fixation failure.[8] Infections are especially linked to open fractures and contribute to a worse prognosis, especially in those cases where it is necessary to remove the hardware in order to treat the underlying sepsis.[38]

Multiple trauma/multiple fractures

A factor which worsens the prognosis of a fracture is also the coexistence of multiple trauma.

The most commonly used evaluation system for a multi-trauma patient is the ISS (Injury Severity Score).[39] The multiple trauma is generally considered as a systemic illness with various levels of involvement of both the musculoskeletal system and the internal organs. On the basis of damage to bones, which may or may not be associated with injuries to other organs, we consider multiple-trauma patients those with an ISS $\geqslant$ 16.[39] On the contrary patients with an ISS < 16 but with more than one fracture could be considered as multiple-fracture patients.

Multiple trauma

Multiple-trauma patients with an ISS $\geqslant$ 16 show especially critical clinical conditions, with important damage to internal organs and the larger vascular sections. This damage may seriously affect the patient's general condition, with a need to treat injuries depending on their severity. Treatment criteria are expressed by Wolf's algorithm (1956), used by many authors and reprocessed by Penning in 1992. This protocol therefore brings about the need to treat the most serious fractures with the main aim of stabilising the patient in the shortest time possible. This sometimes takes place using "invented" means or, more frequently, means that are not suitable for the type of fracture which must be treated and which it is not always possible to remove and replace immediately. Consequently there may be a further worsening of the prognosis of fractures, especially in those complicated by serious damage to surrounding soft tissues. Multiple trauma also brings about large-scale biological damage deriving from the state of shock and high introduction of toxins and free radicals originating from trauma of the solid thoracic and abdominal organs, the large vessels, the head and the spine.

Multiple fractures

Patients with an ISS $\leqslant$ 16 generally have damage to the musculoskeletal system. In these cases the patient is characterised as a multi-fracture patient. In this condition, the critical situation is determined by the consequences coming from the coexistence of several fractures and the severity of these fractures, rather than from injury to internal organs. The multiple-fracture patient can however also be a patient with three or more fractures to the larger segments, without affecting internal organs. This condition is characterised by an ISS $\geqslant$ 16 that represents an emergency as the patient may be in immediate danger of life, due to exsanguination caused by the fractures. In any case, the approach to the multi-fracture patient must be carried out according to the criteria of "early fracture fixation", based on an algorithm used in our Institute, as the stabilisation of the fractures also brings about an immediate improvement in the patient's prognosis and general condition.

The simultaneous occurrence of multiple fractures causes significant problems concerning the treatment strategy and the post-operative rehabilitation period. The fixation of these fractures can be quite demanding and the rates of delayed healing and non-union are raised significantly.

Discussion

Several authors have carried out studies and research on general and local risk factors which could lead to the development of pseudoarthrosis. We must however consider whether there are mathematical models and/or algorithms that help us to understand this pathology. During the 1990s, authors such as Kenwright, Lavini and Renzi Brivio, Calori and Caraffa, Marsh, published important research evidence on bone repair processes after fractures. These authors derived their concepts and intuitions from researchers such as Pauwels (1940s), who overturned the concept of "biological inferiority" of pseudoarthrosis, by proving that in suitable mechanical conditions, the bone tissue is able to complete the biological process of union, identifying the compression agents as favourable forces in relation to the unfavourable ones under stress and torque. Judet in 1958 showed the significance of vascularisation in the pseudoarthrosis setting. He has also indicated that bone sclerosis, which can be seen as opacity of bone fragments in X-rays, is due to an intense inconclusive osteogenetic reaction (hypertrophy) and not to necrosis as had been believed up to that time.[40] Muller, the father of the AO School in 1966, adopted Pauwels' concepts of mechanical stability. He defined as a delayed fracture union the lack of radiologic evidence of healing after 4 months and as pseudoarthrosis after 8 months.[28] Weber and Cech[41] (1976) developed a pseudoarthrosis classification system which is commonly utilised even today in the clinical setting.

The Anglo-Saxon School, with Kenwright, in 1991 reported a monitoring system for fracture union processes, introducing the Orthometer (radiogoniometer) as an instrument for this type of survey, applied to mono-axial external fixators[42]. This instrument allowed the progression of the healing process to be measured quantitatively. The parameter used was the stiffness which is implemented during the evolution of the repair process. This indicator is the exponential sum of constant values and is therefore easy to reproduce. The stiffness value, measured in Nm/degree, increases as healing advances, and Kenwright and collaborators established that functional union (healing) is measured at 15 Nm/degree for a tibia fracture and 20 Nm/degree for a femur fracture.[8]

The Italian School produced another evaluation method of the fracture repair process, called Extensimetry[43]. This is carried out by the extemporaneous application of a strain-gauge bar, supplied with 5 multi-directional sensors, mounted

parallel to the mono-axial Orthofix external fixator. This procedure, as it can distinguish the individual splitting movements of the forces acting on the fracture site axial, angular and torsional, is extremely accurate. It does not require resort to an unfavourable removal (even if temporary) of the external fixator, unlike the Orthometer. The use of this instrument seemed to be more "physiological" from the beginning, superimposable on reality, allowing measurements in both static load (orthostasis) and dynamic mode (walking). It also allowed the possibility of obtaining a graphic curve that shows the evolution trend of the healing process. It offers the advantage of obtaining absolute mathematical numbers and identifying mathematical ratios and indicators, namely: axial indicator (axial load), radial load (torque and bending) and functional indicator (test execution mode). The measurement and comparison of absolute mathematical indicators permitted the study of fracture repair processes in several patients with different types of fractures[43,42]. In whatever way they are carried out, quantitative measurements of fracture healing processes have potential advantages compared to simple manual and X-ray evaluation methods. In 1998, Marsh[2] derived the definition of fracture union as an endosteal or periosteal bone regeneration process, until it reaches the value of 15 Nm/degree for leg fractures, introducing the concept of a threshold value. This was set at the value of 7 Nm/degree and allows the description of a delayed union. If this value is reached by the 20th week one can claim that this fracture will heal due to an endosteal and not a periosteal callus. Finally, the repair must take place within a pre-set period of time. Generally, the time limit is set at 20 weeks, which can normally be accepted so that a fracture shows a tendency to heal. If this does not occur, we have a fracture that does not show a tendency to heal, but does not necessarily lead to a pseudoarthrosis. This should be the optimal stage at which it is necessary to intervene in order to reinitiate or enhance the healing process. On the contrary, on the basis of Marsh's experience, pseudoarthrosis is identified as the evidence of interruption in the formation of periosteal and endosteal callus before the threshold stiffness of 7 Nm/degree is reached.

Conclusions

A variety of risk factors have been identified as contributing to the development of non-union of fractures. Monitoring of the different osteogenetical phases of fracture healing could allow clinicians to predict non-unions at an early stage. Besides morphological criteria like standard radiology and imaging, the authors recommend the introduction of biomechanical tests (Orthometer, Strain-gauge bar or others) as adjuncts to early diagnosis.

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