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Effect of platelet-rich plasma on fracture healing☆

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ABSTRACT

Bone has the ability to completely regenerate under normal healing conditions. Although fractures generally heal uneventfully, healing problems such as delayed union or nonunion still occur in approximately 10% of patients. Optimal healing potential involves an interplay of biomechanical and biological factors. Orthopedic implants are commonly used for providing the necessary biomechanical support. In situations where the biological factors that are needed for fracture healing are deemed inadequate, additional biological enhancement is needed. With platelets being packed with granules that contain growth factors and other proteins that have osteoinductive capacity, local application of platelet concentrates, also called platelet-rich plasma (PRP) seems an attractive biological to enhance fracture healing. This review shows an overview of the use PRP and its effect in enhancing fracture healing. PRP is extracted from the patient's own blood, supporting that its use is considered safe. Although PRP showed effective in some studies, other studies showed controversial results. Conflicts in the literature may be explained by the absence of consensus about the preparation of PRP, differences in platelet counts, low number of patients, and absence of a standard application technique. More studies addressing these issues are needed in order to determine the true effect of PRP on fracture healing.

Introduction

Each year, millions of people sustain a fracture. Although the vast majority of fractures heal uneventfully, approximately 10% of patients experience healing problems with nonunion being the most feared problem [1–5]. Fractures that result in nonunion may result in, sometimes even permanent, functional impairment for the patient. The additional treatment needed also imposes the health care system to tremendous economic burden [3,6].

In order to reduce the risk of nonunion and other adverse healing outcome as much as possible, treatment should be focused on maximizing the fracture healing potential. The process of fracture healing involves an interplay of various biomechanical and biological factors [7]. Bone has the ability to completely regenerate under normal healing condition. Depending on the type of fracture, simple immobilization using a cast or brace may therefore suffice. If additional biomechanical support is needed, intramedullary, screw, or plate fixation can be applied. In situations where the availability of biological factors is judged as (potentially) insufficient (*e.g.*, specific comorbidities, smoking, or open fracture), the biological environment also requires optimization.

In addition to optimizing the patient's condition (*e.g.*, quit smoking, regulation of diabetes), the biological environment can be improved by the introduction of materials with osteogenic, osteoinductive, and osteoconductive properties. If all three properties are needed (*e.g.*, in nonunion or if the defect is large), autograft is the gold standard. However, the limited supply and donor-site morbidity associated with autologous bone grafting have led researchers to explore alternatives like allogenous bone grafting, bone substitutes, demineralized bone matrix, growth factors, recombinant bone morphogenetic proteins, and cell and gene therapy, but these also have their own set of pros and cons [8–19].

Alternative autologous treatments for the induction of fracture healing such as the use of platelet-rich plasma (PRP) has gained popularity in the past years [20]. Studies have shown that thrombocyte-derived growth factors secreted from PRP during fracture healing can trigger angiogenesis and activate proliferation and chemotaxis of mesenchymal cells, osteoblasts, and chondrocytes [21–24]. High concentrations of these growth factors may accelerate bone healing, and a lack of these factors has been hypothesized as being responsible for the development of nonunions. Platelet

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concentrates rich in growth factors therefore in theory represent an osteoinductive therapy for the biological augmentation of fracture healing [21].

The aim of this review was to provide a comprehensive overview of the use of PRP in the treatment of fractures. Details on the preparation and application of PRP as well as the reported effect on radiographic healing and functional recovery are given.

Definition of platelet-rich plasma

In literature, multiple definitions of PRP exist. It is defined as 'an autologous concentrate of platelets suspended in a small volume of plasma' [25]. More specific definitions of PRP are 'a certain volume of plasma that has a platelet concentration severalfold above the physiologic levels' [26] or 'a volume of autologous plasma that has a platelet concentration of 1,000,000 platelets/µl in a 5-ml volume of plasma' [4]. Although these definitions differ, the essence is that PRP is a supraphysiological concentration of platelets.

Plateles – growth factors and role in fracture healing

In case of a fracture, platelets move to the site of tissue injury. Platelets are activated by thrombin and subendothelial collagen, resulting in active secretion of preformed growth factors and other proteins. During platelet activation, the alpha granules within the platelets fuse with the plasma membrane and subsequently release their protein content to the surroundings. The alpha granules contain more than 30 bioactive proteins, many of which contribute to hemostasis and/or tissue healing [21,27–31]. Relevant growth factors for bone healing are platelet-derived growth factor (PDGF-aa, PDGF-ab, and PDFG-bb isomers), transforming growth factor-beta (TGF-β1 and TGF-β2 isomers), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF). They also contain the three proteins fibrinogen, fibronectin, and vitronectin, that are known to act as cell adhesion molecules for osteoconduction and as a matrix for bone, connective tissue, and epithelial migration [21]. Other proteins within the alpha granules include platelet factor 4 (PF4), interleukin-1, platelet-derived angiogenesis factor, platelet-derived endothelial growth factor, insulin-like growth factor (IGF-1), osteocalcin, osteonectin, and thrombospondin-1 [21,30,32–35].

The growth factors and proteins mentioned above trigger angiogenesis, activate proliferation and differentiation of pluripotent mesenchymal cells and osteoblasts, and chondrocytes, and chemotaxis of macrophages [21–25,34,36–41]. Platelets synthesize and release growth factors until additional growth factor synthesis and release is taken over by macrophages.

Clinical evidence for PRP in musculoskeletal applications

For use *in vivo*, PRP can be activated with calcium gluconate or thrombin. Activation with 10% calcium gluconate results in a viscous solution that can be used for percutaneous injection. Activation with thrombin leads to early gel formation and is likely not suitable for percutaneous injection.

PRP has been (successfully) used in a variety of musculoskeletal applications, including spine fusions, cartilage injuries, tendon injuries, and ligament injuries (*e.g.*, rotator cuff repair, lateral epicondylitis and distal biceps tendinopathy) [42–47].

Some studies have shown that PRP increases the healing rate of the nonunion in animal models and humans, suggesting that PRP might stimulate the prematurely terminated bone healing processes [20,48]. Other studies, however, reported that PRP does not give an advantage over placebo or rhBMP-7 [20,49–51]. With nonunion and delayed union as serious complications of fracture treatment, preventing these from occurring is important. The results of exogenous application of PRP in patients with fractures are detailed below.

Clinical evidence for PRP in augmenting fracture healing

PubMed was searched for literature by both authors using search terms and synonyms for fracture and PRP. Only studies available in full text were included. The search resulted in eight clinical studies (704 patients, of whom 403 treated with PRP) [52–59]. Eight studies are randomized studies [52–55,57–59], the ninth study is a cohort study [56] (Table 1).

Almost every study has evaluated the effect of PRP in another fracture type. Fracture types investigated are distal radius fractures [54], scaphoid fractures [53], femoral neck fractures [55], proximal femoral fractures [57], femur fractures [52], combined distal tibia and fibula fractures [56], and calcaneal fractures [58,59].

Only one study mentions a rationale for the use of PRP. Rodriguez-Collazo *et al.* mention that only patients with a poor soft-tissue envelope were enrolled [56]. None of the other studies mention if (or why) biological enhancement of fracture healing may be needed.

Follow-up also varies across studies and ranged from six months [53,54] to six years [59].

Preparation and application of PRP

Growth factors are responsible for the osteoinductive property of PRP. Literature data show there is a lack of standardization in PRP preparation, concentration and individual growth factor concentration. The concentration of each growth factor differs among different patients based on age, gender, platelet count and method of PRP production; however, individual growth factor assays are not performed due to the costs involved [60]. Differences in preparation techniques noted even in FDA approved products [26] may have an impact on the expression of those autologous growth factors [61].

Table 1 provides an overview of the preparation, composition, and application of PRP. Essentially, two processing strategies are used for preparing PRP; some use direct centrifugation either in one step [52] or in two steps [55,58,59], while others use a commercially available device such as the 2-step centrifugation Arthrex ACP system [53], 1-step centrifugation Arthrex ACP system [54], the Arteriocyte Magellan® System [56], or the GenesisCS Component Concentrating System, EmCyte Corporation, Fort Myers, Florida, USA) [57].

Only two studies mention the platelet count in their PRP sample. Liebergall *et al.* mentioned a mean of 1.10×10^9 platelets per concentrate [58], and Wei *et al.* mentioned their PRP sample contained 780,000 platelets per µl [59]. None of the other studies provided details on the cell count, but based on the difference in volume of whole blood versus the final PRP sample it became clear that the fold concentration of thrombocytes in the studies ranged from 2 to 3-fold [54] to 33-fold [59].

In addition to variation in platelet count, the PRP samples used in the included studies also vary in presence of leukocytes and activation prior to use (Table 1). The PRP samples of Griffin *et al.* were the only to contain leukocytes [57]. PRP samples of three studies did not contain any leukocytes [55,56,59], and the other four studies did not report this information [52–54,58].

There is no consensus on the necessity to activate the platelets prior to application. The studies included in the literature review reflect this. Singh *et al.* used thrombin and calcium gluconate in order to active the platelets [52]. Rodriguez-Collazo *et al.* and Wei *et al.* used thrombin and calcium chloride [56,59]. The other

Table 1
Details of studies investigating the effect of PRP including preparation, application, and effects on fracture healing and functional recovery.

Publication	Study design	N patients intervention	N patients control	Fractures	Follow-up	Preparation of PRP	Platelet count	Leukocytes	Activation	Application or PRP (and control)	Union/defect healing	Functional recovery	Main findings
Singh *et al.* (2017) [52]	RCT	n=33 IMN + PRP (=14 closed nailing + PRP injection; n=19 open mailing + PRP gel + fibrin membrane)	n=39 IMN (=16 closed nailing; n=23 open nailing)	Diaphyseal femur fractures	≥6 months	PRP: 70 mL blood from antecubital vein concentrated to 12-14 mL using 2-step centrifugation	N.S. (5 to 6-fold concentrated whole blood)	N.S.	Thrombin (0.2 mL/mL) + calcium gluconate (0.2 mL/mL)	Intervention group 1 (closed nailing): Activated PRP was injected at the fracture site under radiological control. Intervention group 2 (open nailing): fibrin membrane prepared from platelet poor plasma was dipped in liquid PRP. At the end of nailing, PRP was activated until it transformed into PRP gel, which was applied locally at the fracture site intraoperatively. The fibrin membrane was then used to cover and contain the PRP at the fracture site.	Radiological union: 0% at 4 months and 100% at 6 months in each subgroup (p>0.05)	N.S.	PRP has no effect on femoral shaft fracture healing
Namazi & Kayedi (2016) [53]	RCT	n=7 cast + PRP	n=7 cast	Nondisplaced middle-third scaphoid fractures	6 months	PRP: 20 mL peripheral blood concentrated to 1.5 mL using 2-step centrifugation (Arthrex ACP system)	N.S. (13-fold concentrated whole blood)	N.S.	No	Injection of 1.5 mL PRP (saline in controls) into wrist joint Cast for at least 2 months	Intervention: 71% at 2 months, 100% at 3 months. Control: 43% at 2 months, 86% at 3 and 6 months. (p=0.99)	Significantly less pain at rest at 6 months (p=0.03) Significantly better PRWE at 3 and 6 months (p=0.014 and 0.002) No significant difference in wrist motions including radial deviation, ulnar deviation, flexion, and extension at 3 and 6 months	PRP may have a significant effect on pain reduction at rest and amount of difficulty in function

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Table 1 (*continued*)

Publication	Study design	N patients intervention	N patients control	Fractures	Follow-up	Preparation of PRP	Platelet count	Leukocytes	Activation	Application or PRP (and control)	Union/defect healing	Functional recovery	Main findings
Namazi & Mehbudi (2016) [54]	RCT	n=15 percutaneous pinning + PRP	n=15 percutaneous pinning	Intra-articular distal radius fractures	6 months	PRP: 10 mL peripheral blood concentrated to 3-5 mL using 1-step centrifugation (Arthrex ACP system)	N.S. (2 to 3-fold concentrated whole blood)	N.S.	No	Intra-articular injection (radio-carpal joint) of PRP immediately after closed reduction and percutaneous pinning	N.S.	Significant reduction in pain (VAS) and PRWE at 3 and 6 months No significant effect on loss of ROM	PRP may have significant effect on reduction of pain and functional recovery
Samy (2016) [55]	RCT	n=30 cannulated screws + PRP	n=30 cannulated screws	Femoral neck fracture	12-48 months (mean 28 months)	150 mL venous whole blood concentrated to 15 mL PRP, using 2 centrifugation steps	N.S. (10-fold concentrated whole blood)	No	No	PRP was divided on the three screws	Union rate: Intervention: 93% Control: 85% ($p<0.001$) Time to union: Intervention: 3.55 months Control: 4.23 months ($p<0.05$)	HHS (united cases) Intervention: 90 versus Control: 89 ($p=0.093$) VAS (pain) at last FU: Intervention: 41 versus Control: 38 (p-value N.S.)	PRP as adjuvant to cannulated screw fixation increased the fracture union rate and reduced the time to union
Rodriguez-Collazo *et al.* (2015) [56]	Cohort	n=10 cBMA + DBM + PRP + EF	n=10 DBM + EF (historic control)	Closed distal tibia and fibula fracture with a poor soft-tissue envelope	≤18 months	30 mL marrow aspirate (from proximal tibia) and 30 mL whole blood (antecubital vein) were concentrated to 3 mL cBMA and 3 mL PRP using the Arteriocyte Magellan® System	N.S. (10-fold concentrated whole blood)	No	Thrombin + $CaCl_2$	cBMA was mixed with DBM (intervention group). 5 mL DBM was injected percutaneously into fracture site (both groups). After application of Ilizarov fixator, 3 mL PRP combined with calcium chloride and thrombin solution was applied using a spray tip cannula at all surgical wound sites (intervention group)	Intervention:80% complete bone healing at fixator removal (16 weeks) Control: 70% complete bone healing at fixator removal (24 weeks)	N.S.	External (Ilizarov) fixator combined with cBMA, PRP, and DBM expedites fracture healing of the distal tibia and fibula in patients with significant comorbidities. No differences in infection rate or union rate

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Table 1 (*continued*)

Publication	Study design	N patients intervention	N patients control	Fractures	Follow-up	Preparation of PRP	Platelet count	Leukocytes	Activation	Application or PRP (and control)	Union/defect healing	Functional recovery	Main findings
Griffin *et al.* (2013) [57]	RCT	n=101 cannulated screws + PRP n=99 cannulated screws	n=99 cannulated screws	Intracapsular proximal femoral fracture	1 year	PRP was harvested using GenesisCS Component Concentrating System, EmCyte Corporation, Fort Myers, Florida, USA)	N.S. (≥5-fold concentrated whole blood)	Yes	No	Two or three cannulated screws were advanced up to but not beyond the fracture such that no compression was achieved. Upon removal of the guidewire of one screw, 3 mL of PRP was injected through the cannulated screw directly into the fracture site under image intensifier guidance. (drill hole)	Radiographic healing at 1 year: Intervention: 98% Control: 99% (p=1.000) Reoperation within 1 year due to fixation failure: Intervention: 34% versus Control: 40% (p=0.325)	EQ-5D: no difference at 1 year (p=0.799)	No evidence of a difference in the risk of revision surgery within 1 year for the PRP group. Similar union rates and EQ-5D scores at 1 year
Liebergall *et al.* (2013) [58]	RCT	n=12 ORIF (11 IMN, 1 plate) + DBM + MSCs + PRP	n=12 ORIF (10 IMN, 2 plate)	Closed, extra-articular distal tibial fracture	1 year	PRP: 100 mL peripheral blood concentrated to 5 mL using 2-step centrifugation.	Mean 1.10 × 10^9/ concentrate (20-fold concentrated whole blood)	N.S.	No	DBM mixed with MSCs (≥5 × 106/sample) and PRP to a volume of 8 mL, delivered by percutaneous injection under fluoroscopic guidance into the fracture site PRP + MSCs mixed with DBM; injected into the fracture site 3-6 weeks (mean 30 days) after index surgery	Intervention: 100% union, median union time 1.5 months Control: 100% union (3 delayed union), median union time 3 months	No significant difference in SF-12 or pain (VAS)	Intervention with PRP + MSCs + DBM is a safe and efficient therapeutic option; it reduced the time of bone fusion, but had no significant effect on pain or quality of life

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Table 1 (*continued*)

Publication	Study design	N patients intervention	N patients control	Fractures	Follow-up	Preparation of PRP	Platelet count	Leukocytes	Activation	Application or PRP (and control)	Union/defect healing	Functional recovery	Main findings
Wei *et al.* (2012) [59]	RCT	n=85 non-locking plate + allograft + PRP	n=90 non-locking plate + allograft n=101 non-locking plate + autograft	Closed displaced intra-articular calcaneal fractures (Sanders type III)	6 years	100 mL venous blood reduced to 3-5 mL PRP by 2-step centrifuga-tion	780,000/µL (20 to 33-fold concen-trated whole blood)	No	300 IU bovine thrombin + 10% $CaCl_2$	PRP mixed with bone allograft and applied locally during ORIF to fill the void	100% clinical and radiographic healing <12 months without collapse of posterior facet	No difference in pain, walking activities, and function across the groups at 12 months ($p > 0.05$)	Radiographic results of PRP-augmented allograft group similar to autograft group and better than non-augmented allograft group. No effect of treatment of functional recovery

cBMA, concentrated Bone Marrow Aspirate; DBM, Demineralized Bone Matrix; EF, External (Ilizarov) Fixator; EQ-5D, EuroQoL-5D; HHS, Harris Hip Score; IMN, Intramedullary Nail; IU, International Units; MSC, Mesenchymal Stem Cells; N.S., Not Specified; ORIF, Open Reduction and Internal Fixation; PRP, Platelet Rich Plasma; PRWE, Patient-Rated Wrist Evaluation; RCT, Randomized Controlled Trial; ROM, Range of Motion; SF-12, Short Form-12; VAS, Visual Analog Scale.

five studies have not used agents to activate the platelets [53–55,57,58].

Five studies evaluated the effect of only PRP on fracture healing [52–55,57]. The other three studies combined PRP with other potential biological enhancer of fracture repair. Rodriguez-Collazo combined PRP with demineralized bone matrix (DBM) and concentrated Bone Marrow Aspirate (cBMA) [56], Liebergall *et al*. combined PRP with DBM and mesenchymal stem cells (MCSs) [58], and Wei *et al.* mixed PRP with bone allograft [59].

In all studies, PRP was applied locally to the fractures site, but use different procedures to achieve this. Singh *et al.* and Liebergall *et al.* injected PRP at the fracture site under fluoroscopic control [52,58], In a second intervention group. Singh *et al.* injected PRP as a PRP gel (which formed after platelet activation) to cover the fracture site [52]. Namazi & Kayedi as well as Namazi & Mehbudi injected PRP into the wrist and radio-carpal joint, respectively [53,54]. Wei *et al*. mixed PRP with bone allograft and applied it locally during open reduction and internal fixation [59]. The final three studies used less conventional methods to apply PRP. Samy *et al.* mention that they divided the PRP sample on three screws [55] and Grinnin *et al.* injected the PRP through the cannulated screw into the fracture site under image intensifier [57]. Finally, Rodriguez-Collazo *et al.* applied PRP using a spray tip cannula at the surgical wound site [56].

Effects of PRP on fracture healing and functional recovery

The results of the effect of PRP on fracture healing and functional recovery are shown in Table 1. Of the eight included studies, two reported no significant effect of PRP on fracture healing. Both evaluated the effect of only PRP as potential biological enhancing agent. With 100% radiological healing at six months in the intervention and control group, Singh *et al.* found no significant effect of PRP on femoral shaft fracture healing [52]. Similarly, Griffin *et al.* did not find a significant effect of PRP on the fractures healing rate, reoperation rate within one year due to fracture failures, nor on the health-related quality of life (*i.e.*, EQ-5D) in patients with an intracapsular proximal femoral fracture [57].

Three studies, which also only evaluated the effect of PRP, on the other hand, did show an effect of PRP on fracture healing and/or functional recovery.

Samy *et al.* reported that, in patients with a femoral neck fracture, PRP increased the fracture healing rate (93% versus 85% in controls; $p<0.001$) and also reduced the time to union (3.55 months versus 4.23 months in controls; $p<0.05$) [55]. Despite these radiologic results, no significant effect was found on functional recovery as measured with the Harris Hip Score (HHS 90 vs 89 in controls) or pain (41 versus 38 in controls).

Namazi & Kayedi and Namazi & Mehbudi reported that PRP may have a significant effect on pain reduction and functional recovery in patients with a nondisplaced middle-third scaphoid fracture or an intra-articular distal radius fracture, respectively [53,54]. In distal radius fractures, radiographic healing was not reported. In scaphoid fractures, fracture healing in the intervention and control group did not differ significantly (100% versus 86% healing at six months; $p=0.99$).

The three studies that combined PRP with other biologicals all reported added value of the intervention group. Rodriguez-Collazo *et al.* reported that Ilizarov fixator combined with cBMA, PRP, and DBM expedited fracture healing in patients with combined closed distal tibia and fibula fractures with a poor soft-tissue envelope [56]. The overall union rate and infection rate did not differ between the intervention and control group. In another study, Liebergall *et al.* showed that treatment using PRP, MSCs, and DBM reduced the time of bone fusion by 50% (1.5 months versus 3 months in control), however, this had not significant effect on pain or health-related quality of life (Short Form-12, SF-12) [58]. In patients with a closed displaced intra-articular calcaneal fracture (Sanders type III), Wei *et al*. showed that the PRP-augmented group had the same union rate as patients treated with an autograft [59]. They also could not demonstrate an effect of PRP on functional recovery until 12 months after trauma.

Discussion

This is the first comprehensive overview of the use and effect of PRP in the initial treatment of fractures [52–59]. It provides details of seven RCTs and one cohort study on the preparation and application of PRP as well as the reported effect on radiographic healing and functional recovery. The follow-up of all studies was sufficient for reporting a reliable rate of fracture healing.

Overall, the number of available and included studies is low. Moreover, half of the studies had a limited sample size [53,54,56,58]. Each study investigated the effect of PRP in another population and included a different type of fracture. Only one study reported that all enrolled patients had a poor soft-tissue envelope [56]. None of the other studies mention if the biological factors that are needed for fracture healing were deemed inadequate or not.

There was also substantial heterogeneity across studies regarding the preparation, composition, and application of PRP. This makes it impossible to conclude on requirements for clinical effectiveness of PRP. As far as details are provided, the platelet concentration and presence of leukocytes are different in each study. If PRP was activated, thrombin was used in combination with either calcium gluconate or calcium chloride [52,56,59]. The effect of PRP was also difficult to assess, since each study applied it differently. The three studies even used PRP in combination with other compounds with potential osteoinductive properties [56,58,59]. From these studies it is unclear if clinical results were attributable to PRP or the other compound(s).

Only two studies applied the total PRP sample at the fracture site under fluoroscopic control [52,58]. Other studies sprayed PRP on the wound site [56], injected it into the joint [53,54] or through a cannulated screw [57], or divided it on the surface of screws [55]. It is unlikely that the desired amount of PRP actually reaching the fracture site in the latter studies was sufficient for stimulating fracture healing.

Despite the limitations mentioned above, PRP can be applied safely as adverse events hardly occur. Two studies reported that PRP reduced the healing time [55,58]. Only one study showed an increased healing rate in the PRP group [55]. A positive effect of PRP on functional outcome or pain was found in two studies [53,54]. The high union rates in the control group of most studies require a large sample size in order to demonstrate that PRP is able to improve fracture healing.

Based on the above, the routine use of PRP to improve fracture healing rates cannot be recommended on the basis of the present literature. Future controlled studies with larger sample sizes and better standardized (and reported) use of PRP are needed in order to determine the true effect of PRP in optimizing patient care with respect to bone healing.

Conclusion

Several studies, mostly RCTs, have investigated the role of PRP in fracture treatment. Controversial results were obtained. Conflicts in the literature may be explained by heterogeneous study populations as well as by the absence of a consensus about the preparation of PRP, required platelet counts, and application technique. Therefore, the routine use of PRP to improve fracture healing rates cannot be recommended on the basis of the present literature.

Ethics

Ethics Committee approval is not applicable to this review.

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Declaration of Competing Interest

The authors (Esther M.M. Van Lieshout and D. Den Hartog) declare that they have no conflict of interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2020.12.005.

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