Fracture healing in the elderly: A review

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Abstract

Older patients are commonly at a higher risk of experiencing a bone fracture. Complications during fracture healing, including delayed union and non-union, can arise as a result of a multitude of patient and treatment factors.

This review describes those factors which contribute to a greater risk of the development of non-union with particular reference to the elderly population and discusses therapies that may enhance the fracture healing process in hopes of reducing the incidence of delayed union and non-union.

Increasing age does seem to increase the risk of delayed union or non-union. In addition, smoking and the treatment of post-fracture pain with NSAIDs put the patient at the greatest risk, while ultrasound therapy appears to be a non-invasive, effective treatment option to reduce the risk of delayed or non-union. Use of growth factors, stem cells and role of surgery is also discussed.

Keywords

Fracture healing; delayed union; non-union; elderly

Introduction

Bone fractures are common in the elderly, with residual lifetime fracture risk in a person aged 60 years reported to be 29% in males and 56% in females [1]. During normal fracture healing, an intricate series of physiological events results in the formation of new bone with structural and mechanical properties similar to that of the original, intact bone [2]. This process results from the release of inflammatory cytokines and growth factors and the migration and differentiation of mesenchymal progenitor cells at the site of injury. Bone healing can be simplified into three successive stages: inflammation, repair, and remodelling. The fracture disrupts the continuity of the bone and ruptures blood vessels, leading to the immediate formation of a clot and the release of biochemical messengers at the fracture site. This results in granulation tissue formation with migration of inflammatory and mesenchymal progenitor cells. During the repair stage, callus develops in which progenitor cells differentiate into either chondrocytes or osteoblasts to deposit cartilage or woven bone, respectively, across the fracture site. Finally, remodelling occurs over a period of months to years during which the callus is modified and replaced by lamellar bone [3].

The normal healing time of a fracture varies from 4 weeks to more than 16 weeks depending on the location, the mechanism of injury, and the degree of soft tissue disruption. In addition, there are a number of intrinsic and extrinsic host factors which are associated with delayed union [4]. In these cases, one or more stages of the healing process are impaired compared to healthy patients, requiring pharmacological or surgical intervention to improve healing rates.

The prevalence of delayed healing and non-union varies greatly between studies, with reported incidence as low as 1% and as high as 54% [5]. In a review of tibia fractures, Phieffer et al. combined the results of 22 studies and found that, among 5517 fractures, 2.5% progressed to non-union while 4.4% underwent delayed union [6]. Such healing complications are a burden for both the patient and the healthcare system. Patients suffer due to a lack of functional healing and are often unable to return to work or to perform activities of daily living. Antonova et al. found the median cost of care for patients in the USA with non-union to be US$25,556 compared to $11,686 for patients without non-union [7], while Patil et al. calculated a direct healthcare cost of nearly £30,000 for treatment of each patient with non-union [8]. Patients are also more likely to be prescribed strong pain medications such as opioids and to require opioid therapy for significantly longer than patients without non-union [7]. Although many cases of delayed union and non-union are idiopathic in nature, several reports have suggested that these complications are more common in the elderly [9,10,11].

The aim of this literature is to investigate the effect of patient characteristics, such as age and comorbidities, on poor fracture healing and to recommend clinical strategies that could lower the incidence of delayed union and non-union.

Methods

A literature search was performed using PubMed and Google Scholar with the key search terms “fracture healing”, “delayed union”, “non-union”, “the elderly”, “pharmacological effects”, “smoking”, “diabetes”, and “acceleration”. Selection criteria for inclusion in this review are as follows: (1) delayed union and/or non-union are the primary clinical outcomes being measured; (2) the study states how it defined delayed union or non-union; (3) a minimum study population of 20 subjects (i.e. no case studies were included); (4) in clinical studies, a minimum patient follow-up time of 12 months; (5) the study is written in English.

Definitions

There are no clear-cut definitions for non-union and delayed union; because of this, diagnosis can be subjective and varies with the fracture pattern. Methods of diagnosis include radiographic

examination, functional considerations (e.g. pain free on weight bearing), or comparison to a control group depending on the diagnosing author or physician. Due to this lack of congruity across studies inspecting delayed union and non-union, this review includes the results of each study based on its own definitions of these healing complications. For clinical studies reported in this review, delayed union is defined as a statistically significant difference in fracture healing times between a group of patients sharing a characteristic (e.g. age above 70 years or smokers) and a control group of healthy patients. A diagnosis of non-union was determined by a lack of radiographic improvement.

Age, lifestyle, and comorbidities and bone healing

Age: With increased age, the majority of the population undergoes physiological changes, such as the development of osteoporosis, that leave them more susceptible to fractures and subsequent healing complications [9]. This is particularly true of female patients post menopause. However, few large clinical studies have examined the influence of age alone on the rate of bone healing after a fracture. Nikolaou et al. conducted a study which found that patients aged 65 years and above have significantly longer healing times than patients aged 18-40 (19.38 weeks vs. 16.19 weeks, respectively) [12]. However, all patients in the elderly group showed radiographic signs of osteoporosis compared to none in the younger group and the female to male ratio was significantly higher in the elderly group. Thus, the study was inconclusive as it did not determine whether ageing, osteoporosis, gender, or a combination may contribute to a delay in healing. In other studies, increased age was correlated to healing complications in tibial shaft [13], clavicle [14], and femoral neck [15] fractures and floating knee injuries [16].

Delayed healing in elderly patients has been attributed to a lower capacity for mesenchymal progenitor cell division and differentiation, impaired angiogenesis, and reduced levels of growth factors with increased age [9]. These findings have been shown in various animal models. Several studies examining the biomechanical progression of fractures have shown that elderly rats require more time to regain full mechanical strength compared to young rats [17,18,19]. Lu et al. observed the molecular, cellular, and histological progression of tibia fractures in juvenile, middle-aged, and elderly mice and found that young mice showed earlier signs of chondrocyte maturation, vascular invasion, and bone formation at the site of the fracture than elderly mice [11]. The results suggest that enhancing cell differentiation and improving osteoblast function may be key targets for accelerating bone healing in the elderly.

While there is some evidence that elderly patients are at a higher risk of delayed union or non-union after a fracture, a number of studies have found no connection between age and healing complications [20,21,22]. In fact, in a study by Hernandez et al., patients aged 65-79 years were less

likely to undergo healing complications than patients aged 18-29 years [20]. This may be attributed to younger patients experiencing more traumatic, higher-impact fractures than patients in the older group. Liu et al. found a trend toward significance with age as a predictor of non-union in midshaft clavicular fractures, but it was not independently a predictive risk factor following multivariate analysis [21]. More clinical studies examining the progression of fracture healing in humans will need to be performed to determine whether age alone plays a significant role in the development of these costly conditions.

Smoking: Smoking is known to cause a number of health complications, and recent studies suggest that it can also delay or inhibit fracture healing. Patients who smoke often have diminished bone mineral density (BMD) [23], leaving them at a higher risk for fractures. Smokers are also at a high risk of developing atherosclerosis and low blood-oxygen levels, leading to poor perfusion and the deposition of fibrous tissue rather than bone at the fracture site. There is some question as to whether the smoke products from cigarettes are the main contributors to fracture healing disorders or if nicotine alone can impair bone repair. Donigan et al. found that rabbits exposed to nicotine transdermally have calluses with decreased mechanical strength and a higher rate of non-union compared to rabbits given saline [24]. Conversely, Skott et al. showed that nicotine administration in rats shows no difference in fracture healing rates compared to a control group [25]. Currently, no clinical studies have been performed to show the effects on fracture healing of nicotine replacement therapies or electronic cigarettes.

In clinical studies, smoking is one of the biggest predictors of delayed fracture healing. In a study of 50 smokers and 50 non-smokers who underwent a two-level spinal laminectomy and fusion, 40% of smokers developed a non-union after 1 to 2 years compared to just 8% of non-smokers [26]. Schmitz et al. tracked the progression of tibial shaft fracture healing in 76 smokers and 70 non-smokers and found that the median time to clinical healing was 269 days in smokers compared to 136 days in non-smokers [27]. In the same study, radiographic healing was found to be delayed by 69% in the group of patients who smoked compared to those who did not smoke. Similar results have been produced by several other studies [21,28,29,30,31].

The cessation of smoking has been shown to be of benefit to fracture union. Cook et al. showed that patients who stopped smoking 10 or more years prior to presenting with a fracture healed as fast as patients with no prior history of smoking [32]. Others have suggested that stopping smoking during healing may promote union [33], but more studies will need to be performed to elicit the benefits of cessation immediately after a fracture. Overall, it is important that physicians know the negative effects of smoking on fracture healing and advise their patients accordingly.

Diabetes mellitus: Diabetes mellitus is increasingly prevalent in the global population and research continues to reveal its pathological effects on various physiological processes. Many diabetic patients have poor blood sugar control and suffer prolonged periods of hyperglycaemia with advanced glycation end product formation, increased reactive oxygen species, and chronic inflammation, all of which have a deleterious effect on the formation of bone [34]. These factors contribute to the formation of greater numbers of osteoclasts and induce apoptosis of osteoblasts, leading directly to the loss of bone and increased susceptibility to fracture. When fractures occur in a diabetic patient, osteoblast differentiation from migratory mesenchymal cells is inhibited which results in delayed union or non-union due to reduced bone formation.

Clinical studies have supported the theory that people with diabetes are at a high risk of experiencing fracture healing complications. Glassman et al. compared the course of healing in 51 non-insulin-dependent diabetic, 43 insulin-dependent diabetic, and 43 control patients after undergoing lumbar fusion [35]. Patients in the control group were matched to both diabetic groups with regards to age, gender, smoking status, level of fusion, and operating time and blood loss. The study found that 22% and 26% of non-insulin-dependent and insulin-dependent patients, respectively, developed non-union, compared to 5% of control patients. A study performed by Loder found a prolonged healing time (163% of expected time to union) in a group of 31 diabetic patients with lower extremity fractures [36].

At even higher risk of undergoing complications during fracture healing are diabetics with comorbidities such as nephropathy, neuropathy, or vascular disease. Jones et al. compared fracture healing in 21 patients with diabetes with comorbidities to 21 diabetics with no known comorbidities and found that 47.6% of comorbid diabetics and 19.7% of non-comorbid diabetics developed complications [37]. Complications in this study included development of infection or non-union and the need for long-term bracing or amputation. This result has been reproduced by Wukich et al [38]. In diabetic patients with fractures, the risk of developing healing complications can be minimized by close control of blood glucose levels during healing [39].

Drugs affecting bone healing

NSAIDs: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in both inpatient and outpatient settings to relieve pain. NSAIDs act as an inhibitor of cyclooxygenase, which is involved in the production of pro-inflammatory prostaglandins. These prostaglandins are known to play a role in the regulation of bone formation [40]. By limiting the production of these important signalling molecules, NSAIDs may cause a delay in the formation of new bone during fracture healing [41]. A large number of both laboratory and clinical studies have supported this claim. Altman et al.

produced femoral fractures in rats given NSAIDs and in control rats and examined the histological and mechanical properties of bone at 2-week intervals up to 12 weeks post-fracture [42]. Half of the group that received NSAIDs were given the drugs for only 4 weeks, while the other half was given therapy for the duration of the study. The rats in both therapy groups showed significantly lower mechanical strength at 10 and 12 weeks compared to the control rats, indicating that even immediate NSAID use after a fracture causes a delay in bone formation. This result has been repeated in other animal studies [43,44,45].

In humans, delayed union with NSAID use has been demonstrated by Butcher et al [46]. In 94 patients with a tibial fracture, those who took NSAIDs during the course of healing experienced an average delay in union of 7.6 weeks compared to patients with no exposure. The group who experienced a delay included patients who took NSAIDs both as a single dosage and multiple doses, indicating that just one exposure can produce complications. Patients exposed to NSAIDs were found to be at a high risk of delayed union or non-union in a study examining long bone fractures [30] and in a study examining fractures throughout the body [47].

Corticosteroids: Corticosteroids are used in a variety of applications including inflammation control and immunosuppression. While these drugs are effective in a variety of clinical scenarios, long-term use of corticosteroids has been associated with the development of osteoporosis and increased risk of fracture [48] due to its promotion of apoptosis of osteoblasts and osteocytes in bone [49]. Due to their negative effect on bone formation in healthy bone, there is some concern that corticosteroids may cause delayed union in the healing of fractures.

Although studies examining corticosteroids' effect on fracture healing in humans are limited, a number of animal studies have been published. Blunt et al. observed fracture healing in rabbits histologically and found that both new blood vessel and callus formation were lessened in rabbits receiving cortisone [50]. Similarly, Waters et al. found that 3 out of 20 rabbits given prednisone achieved union 6 weeks after fracture compared to 13 out of 16 that did not receive corticosteroid therapy [51]. Other studies have found no inhibitory effect of corticosteroid therapy on fracture healing [52,53,54]. Due to the conflicting results found in animal studies, clinical studies in humans should be performed to determine the effects of corticosteroids, if any, on bone healing.

Bisphosphonates: The use of bisphosphonates has been indicated in patients with osteoporosis. Their mechanism of action involves the inhibition of osteoclasts, thereby preventing bone resorption. In theory, their use leads to stronger, denser bone; however, there are concerns that resorption is necessary to prevent the accumulation of microdamage and a subsequent increase in risk of fracture [55]. With growing numbers of patients presenting with subtrochanteric fractures

after chronic use of bisphosphonates, there is some evidence that prophylactic intramedullary nailing of the contralateral femur showing a nondisplaced stress fracture prevents progression to a complete, displaced fracture [56].

There is controversy as to whether bisphosphonates may inhibit healing after a fracture, but few clinical studies exist. Lyles et al. followed 1065 patients receiving zoledronic acid, a potent bisphosphonate administered once yearly, and compared them to a group 1062 patients receiving a placebo after hip fracture [57]. In the group receiving zoledronic acid, rates of any new clinical fracture were 8.6% compared to 13.9% in the placebo group, representing a 35% reduction in recurrent fracture risk in those patients receiving bisphosphonates. Another study performed by Solomon et al. retrospectively reviewed the risk of non-union after humerus fracture [58]. The study found that the patients receiving bisphosphonates in the post-fracture period had increased odds of developing a non-union compared to those who did not (odds ratio, 2.37). In a review which compiled the results of several studies examining the effects of bisphosphonate use after fracture, Molvik found that bisphosphonates significantly delay the union of distal radius fractures, but not femoral fractures [59]. Due to the lack of clarity in the results of clinical studies performed to date, it is recommended that more prospective studies take place and that physicians are aware of the possible risk of delayed union when prescribing bisphosphonates to patients with fractures.

Anticoagulants: Anticoagulants are often prescribed following surgery to prevent deep vein thrombosis and are also used to prevent strokes and adverse events in the heart. Although effective in certain conditions, there are definite risks to their use as the process of blood clotting is inhibited in patients taking them. Because the formation of a clot at the fracture site is one of the first steps in fracture healing, there is some speculation that anticoagulants may delay or inhibit the healing process when fracture occurs. In animal studies, the effects of anticoagulants on fracture healing have been unclear. In a study published by Stinchfield et al. in 1956, the use of anticoagulants in the preoperative period resulted in delayed union in both rabbits and dogs, while administration in the postoperative period resulted in fibrous, rather than bony, union [60]. Some laboratory studies since then have produced similar results, while others have found that no inhibitory fracture healing effects are elicited by the use of anticoagulants [41].

The approvals of newer anticoagulant therapies such as low molecular weight heparins (LMWH) and rivaroxaban have revived interest in their effects on fracture healing. Say et al. evaluated the effects of four LMWHs, enoxaparin, nadroparin, dalteparin, and fondaparinux, on femoral fractures in rats [61]. None of the anticoagulants inspected showed radiographic or clinical difference compared to the group that received placebo injections. Histologically, fondaparinux was associated with

increased callus formation compared to the control group, while the remainder showed no significant difference. A review similarly found no evidence that LMWH affects bone healing [62]. A study comparing enoxaparin, a subcutaneously administered LMWH, to rivaroxaban, an oral anticoagulant, found that enoxaparin is associated with decreased levels of early osteogenic markers in mesenchymal progenitor cells, while rivaroxaban produced no effect [63]. In a follow up study, Klüter et al. found no inhibitory effects of rivaroxaban on the healing of femur fractures in rats [64].

Because of the lack of congruence in laboratory results to date, large clinical studies will need to be performed examining the effect of anticoagulant therapy on fracture healing. Until more definitive results are produced, physicians should be aware of a possible link between the use of anticoagulants and impaired fracture healing.

Promotion and acceleration of bone healing

Although fracture healing complications have been linked to a number of patient characteristics and pharmacologic interactions as previously mentioned, recent studies have focused on strategies to reduce the risk of delayed union and non-union. The majority of these therapies are initiated after fracture occurs and have showed promise as accelerators of bone union. The further investigation and use of these may prove to be essential for use in patients who are at a high risk of delayed union.

Ultrasound: Low-intensity pulsed ultrasound has long been investigated for its potential to induce fracture and wound healing. Harrison et al. recently described the mechanism by which ultrasound can accelerate fracture healing [65]. The application of ultrasound produces nanomotion at the fracture site with frequency and amplitude directly correlated to the characteristics of the ultrasound. As a result of this mechanical stimulation, various signalling pathways are activated, one of which leads to increased production of cyclooxygenase and pro-inflammatory prostaglandins. These consequently lead to enhanced mineralization and stability at the fracture site.

Clinical studies have widely supported the view that the application of ultrasound has enhancing effects on fracture healing. Cook et al. demonstrated the profound effects ultrasound can have on both smokers and non-smokers who have fractures [32]. In 67 patients with tibial fractures (33 receiving active ultrasound, 34 treated with a placebo device), ultrasound was linked with a 41% reduction of healing time in smokers and a 26% in non-smokers. In the same study, distal radius fracture healing was reduced by 51% in smokers and 34% in non-smokers who received active ultrasound therapy compared to the placebo device. Furthermore, no significant differences were noted between healing the times of smokers and non-smokers who were treated with ultrasound

therapy. Similar results have been published by Liu, who found patients receiving ultrasound therapy throughout the course of distal radius fracture healing had a healing time of 32 weeks, while a group receiving placebo therapy healed in 40 weeks [66].

Overall, ultrasound is a safe, non-invasive therapy that has shown promise in decreasing healing time and reducing the risk of non-union after fracture [67]. Because of its proven efficacy and its lack of known contraindications, ultrasound therapy should be considered for all patients who are recovering from a fracture regardless of the presence of any conditions that may inhibit union.

Bone morphogenetic protein: Bone morphogenetic proteins (BMPs) are recognized as the key regulator of osteogenesis and skeletal repair after a fracture occurs [68]. They are involved in the recruitment of mesenchymal progenitor cells to the fracture site and in the differentiation of these cells into osteoblasts. Because of these effects, the administration of recombinant human BMPs (rhBMP) during fracture healing has been studied extensively. In a study of 450 open tibial fractures, intramedullary nail plus rhBMP treatment was associated with a 44% reduction in the risk of non-union, significantly faster fracture healing, and fewer hardware complications than the use of the intramedullary nail alone [69]. The rhBMP was administered after being applied to an absorbable collagen sponge implanted at the fracture site. A similar result has been reproduced by Wei et al [70].

Due to the expensive nature of BMP supplementation during the healing process, several have questioned whether their widespread use reduces the healthcare costs related to non-union and delayed union. Wei et al. found that BMP use in open tibial fractures led to a net cost reduction of nearly $6000 per patient [70]. BMP therapy was only used with grade IIIA and B fractures and resulted in fewer secondary interventions. Alt et al. calculated both direct and indirect (i.e. patient productivity losses) healthcare costs and found that BMP therapy was associated with cost savings in the same severe tibial fractures [71]. It is therefore recommended that only those patients at a high risk of non-union and those with severe fractures are treated with BMP.

Teriparatide: Teriparatide is a recombinant human parathyroid hormone with an anabolic effect on bone and its use is associated with increased osteoblast activity and bone mass [72]. Due to these effects, administration of teriparatide therapy during fracture healing has recently been investigated. Huang et al. studied the effects of teriparatide use after intertrochanteric femoral fracture on osteoporotic patients [73]. The study found that postoperative teriparatide therapy was associated with a reduction in healing time and an improved functional outcome score compared to patients who did not receive therapy. In addition to this study, there are many case studies reported on the safety and efficacy of teriparatide use in accelerating bone repair. However, large clinical

trials with definitive results are necessary prior to its recommendation in the treatment of all fractures.

Vitamin D and calcium: Vitamin D and calcium supplementation have been used as a treatment in patients to reduce the risk of osteoporosis and subsequent fractures, but their efficacy is uncertain. Tang et al. showed that patients treated with vitamin D and calcium showed a 12% risk reduction in fractures of all types and a significant increase in BMD [74]. Conversely, Jackson et al. showed that although treatment provided a small increase in BMD, the risk of fracture was not reduced and the risk of developing kidney stones increased [75].

Due to their potentially beneficial effect on BMD, there is some question as to whether supplementation with vitamin D and calcium may accelerate fracture healing or prevent non-union. Doetsch et al. studied the effect of supplementation in patients with proximal humerus fractures and found that patients being actively treated with vitamin D and calcium had a higher BMD at 6 weeks than those receiving a placebo [76]. However, more studies are needed to determine if a higher BMD leads to a more stable fracture or earlier clinical or radiographic healing. In a different study, Boszczyk et al. compared vitamin D concentration in patients who experienced non-union and patients with normal fracture healing [77]. The study found no difference in the prevalence of vitamin D deficiency in the two groups. Overall, vitamin D and calcium supplementation appear to have a limited effect, if any, on the rate of fracture healing and patients receiving supplementation should be closely monitored for signs of kidney stone development.

Surgical intervention: When treating fractures surgically, care should be taken to preserve as much periosteum and surrounding soft tissue as possible so as to minimize the risk of future delayed or non-union [78]. When non-union occurs after fracture as evidenced by a lack of clinical and radiographic healing progression, a number of surgical treatments are available. These include internal fixation via plates, screws, or intramedullary nailing; external fixation; and implantation of autologous bone, cadaveric bone, or synthetic bone at the fracture site. Achieving primary stability and in addition promoting local blood supply with the help of vascularised flaps in cases of atrophic non-union are key elements to ensure bony union in these technically challenging cases.

Stem cells: There is increasing evidence that the injection of autologous mesenchymal stem cells (MSC) at the site of an established non-union promotes bone healing. In these procedures, stem cells are typically harvested from the anterior iliac crest of a patient, concentrated in vitro, and injected at the site of a non-union in the same patient. Hernigou et al. found that this procedure resulted in the union in 53 out of 60 established non-unions [79]. In this study, the 7 non-unions that failed to heal were injected with a significantly lower concentration of progenitor cells than

successful treatments, indicating that a threshold exists for efficacy of the procedure. Connolly et al. achieved similar results using a combination of either cast immobilization or intramedullary nailing with MSC injections, healing 18 of the 20 established tibial non-unions studied with this technique [80]. Although evidence suggests this procedure can be successful in the treatment of non-unions, it is particularly costly due to its highly demanding laboratory culturing technique [81].

Growth factors: After a fracture occurs, the expression of various growth factors is upregulated at the fracture site, playing an important role in the promotion of healing. Some laboratory studies have examined the effect of applying growth factors at the site of a fracture in order to accelerate healing. Geiger et al. studied the effect of vascular endothelial growth factor (VEGF) application to implanted collagen sponges at the site of critical size bone defects in rabbits [82]. Rabbits in the control group showed no new bone formation, whereas rabbits treated with VEGF showed significant bone deposition. VEGF is a biomarker that promotes angiogenesis, resulting in the reestablishment of vascular supply at the fracture site [83]. Similar results have been achieved by the application of fibroblast growth factor at the site of a non-union in primates [84] and a combination of insulin-like growth factor and transforming growth factor-β at the site of a fracture in rats [85]. Although various growth factors have shown promise as promoters of fracture healing, clinical studies in humans should be performed to assess their safety and efficacy.

Conclusions

The risk of fracture in the elderly population is high due to the common development of conditions such as osteoporosis that weaken the structure of bones. When fractures occur, healing complications can arise as a result of both intrinsic and extrinsic patient factors. Some of these are factors over which either the patient or physician has control, such as alleviation of pain with NSAIDs, while others cannot be changed, such as gender and age. Physicians should inform their patients who present with a fracture of ways in which to minimize the risk of delayed healing, such as the cessation of smoking, and keep in mind therapies such as ultrasound that may promote healing. In any case, it is of great importance that physicians be able to identify patients who are at risk of delayed union or non-union and use this knowledge to best manage treatment.

Contributors

Bradley A. Foulke reviewed the literature and prepared the manuscript, Adrian R. Kendal reviewed and edited the manuscript, David W. Murray supervised the study and Hemant Pandit supervised the study and reviewed and edited the manuscript.

Competing interest

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