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Review Article

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DRUGS AND FRACTURE HEALING: A REVIEW OF LITERATURE

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Fracture healing is a physiological process by which bone regenerates itself following injury. It occurs through five stages: haematoma, inflammation, callus formation, consolidation and remodeling[1,2]. These stages are not sharply demarcated and that two or more stages may be seen at same time in different parts of bone[3].

The healing process can be influenced by a wide variety of factors in both directions; augmenting or delaying. The augmenting factors of fracture healing can be described under biological (e.g. autogenous bone graft)[4], mechanical (e.g. cyclic loading on fractured bone)[5], biophysical (e.g.electro-magnetic stimulation)[4] and pharmacological factors; the subject of this review.

On the other hand, factors delaying fracture healing include patient factors (e.g. malnutrition, anaemia and diabetes mellitus)[6], fracture characteristics (e.g. diaphysial frac-ture distal to entry of the nutrient artery takes more time to heal than metaphysical fracture)[7], orthopaedic treatment (e.g. inade-quate immobilization and repeated manipulation)[8], and also different pharmacological factors.

Effect of prostaglandins and inhibitors of their synthesis (non-steroidal anti-inflammatory drugs; NSAIDs) on fracture healing:

(A) The role of prostaglandins (PGs):

Prostaglandin production and COX-2 mRNA are increased in fracture callus during the first two weeks following injury, suggesting a role in the early phase of bone healing[9]. The production of COX-2 metabolites during the inflammatory phase is required for efficient bone healing and that mesenchymal cell differentiation is a major target of cyclo-oxygenase activity. Under basal conditions, COX-2 activity maintains a population of mesenchymal stem cells in a preosteoblast state responsive to additional osteoblastic signals. During injury, the elevated COX-2 expression increases the osteoblastic potential of mesenchymal stem cells and supports their differentiation to osteoblast in response to osteogenic signals[9].

Dekel et al[10] conducted a study in which the investigators measured the release of PGs from muscle and bone in fractured rabbit tibias. The results demonstrated that, in comparison to the undamaged control tibias, the fractured tibias released

significantly more prostaglandin E and prostaglandin F as early as three days following fracture, suggesting that increased production of PGs serves as one of the responses of bone and muscle to trauma. Classically, a combination of redness, warmth, swelling, and pain serves as the characteristic signs of inflammation. Experimental investigations over the past several decades have elucidated a role for PGs in each of these key aspects of inflammation, thus producing a direct link between PGs and inflammation[11].

Higgs et al[12] examined the role that PGs play in attracting additional inflammatory cells to sites of phagocytosis and inflammation and they concluded that PGs might possess a chemotactic affinity for polymorphonuclear leukocytes (PMNs) at sites of inflammation. Regarding the role of PGs in bone healing, Dietrich et al[13] stated that PGs caused an increase in the actual number of osteoclasts, so they served as powerful stimulators of bone resorption. In addition to that, Lin et al[14] concluded that PGs enhanced bone formation via an increase in the osteoblast concentration.

Local infusion of PGE_2 for 6 weeks on a plated unilateral osteotomy in rabbits caused a dose-dependent stimulation of callus formation and increased total bone mineral content[15]. PGE_2 was also infused into the anterior tibial periosteum of the right leg of rabbits for 6 weeks. It resulted in the formation of primitive woven bone and in muscles the formation of connective tissue[16].

Non-prostanoid EP_2 receptor-selective PGE_2 agonist injected into the proximal tibial metaphysis of the rat, dose-dependently stimulated local bone formation[17,18].

(B) Effect of NSAIDs

Over the past two decades**,** many studies using animal models of fracture healing have reported inhibitory effects of various NSAIDs on skeletal repair[19]. NSAIDs delay bone healing, probably through their prostaglandin inhibitory action[20]. There are many individual variations between NSAIDs regarding their inhibitory effects on fracture healing.

A recent human study examined features associated with non-union of the femoral shaft and included 32 patients with non-union of fractured femur and 67 comparable patients with united fracture. They found that there was a marked association between non-union and the use of NSAIDs[21].

Aspirin

There was a dose-related retardation of healing of fractured right radius and ulna of the rat which was statistically significant only at the highest level of aspirin[22]. Aspirin injected intramuscularly (25mg/kg/day), resulted in a significant inhibitory effect on fracture healing of fractured rabbit tibia when given for 14 days, but no significant effect was found when administered for 2 days[23].

Diclofenac

Diclofenac given intramuscularly for 7-10 days to rats with closed diaphyseal fracture of the right tibia, clinically inhibited fracture healing at 2 weeks but not at 4 or 6 weeks postfracture[24]. Similarly, oral administration of diclofenac twice daily for 21 days significantly delayed fracture healing in rats (operated on by transverse osteotomy of proximal tibia of the left leg and measured by x-ray, CT scan, 3-point bending and histology)[25]. In vitro, diclofenac significantly decreased the proliferation of human osteoblast at concentration probably reachable in vivo (6mg/ml)[26]. Diclofenac injected intra-

muscularly in rabbits inhibited healing of fractured tibia when given for 14 days and assessed by radiological and histological means, but no significant effect on fracture healing was found after being administered for 2 days only[23]. However, the effect of combined diclofenac and aspirin treatment seems to be synergistic, producing a significant delaying effect when assessed histologically even after 2 days of treatment[23]. Another NSAID related to diclofenac (ketorolac) delayed the healing of simple, closed transverse fractures in male rats[27].

Ibuprofen and Naproxen

Ibuprofen (30mg/kg/day) orally for 4 or 12 weeks inhibited repair of femoral fracture in rats when assessed by mechanical and histological examination. This effect was not reversible after cessation of ibuprofen[28]. Ibuprofen at doses of 17 and 34mg/kg daily also inhibited bone healing of grooves made in both right and left mandibular condyles of the rabbit[29]. Naproxen blocked bone resorption in the cancellous bone of the proximal tibial metaphysis of the rat by slowing osteoclast activity at a dose ranging from 2 to 32 mg/kg/day[20]. Naproxen also impeded new bone growth when given orally for 4 weeks in rabbits[19].

Indomethacin

Indomethacin orally (2mg/kg/day) seriously impaired the healing of femoral fractures assessed by mechanical, radiological and histological methods[30]. Allen et al[22] also found that indomethacin at all dose levels tested (1,2 and 4 mg/kg/day) retarded healing of fracture right radius and ulna in rats. Moreover, indomethacin was found to inhibit healing of intramedullary pinned osteotomies and also non-displaced unilateral fractures of the femur in rats under both stable and unstable conditions when assessed 4-6 weeks after surgery[16,31]. The inhibitory effect of indomethacin (1mg/kg/day, orally)on fracture healing in rats was found to be reversible after cessation of treatment[32]. In rabbits, indomethacin (10mg/kg) was also shown to decrease the bone mineral content and maximum bending strength of tibial osteotomies fixed with a small metal plates[33]. On the other hand, in selected clinical situations, inhibition of bone formation can be clinically useful as in preventing heterotopic ossification[34,35]. Patients with concurrent fractures of the acetabulum and long bones who received indomethacin to prevent heterotopic ossification, have a significantly greater risk of non-union of the fracture of the long bones compared with those who received radiation or no prophylaxis[36].

COX-2 inhibitors

Rofecoxib oral administration to rabbits decreased new bone formation in the tibia in a similar way to non-specific NSAIDs as naproxen[19]. The healing of tibia fractures in mice was significantly delayed by COX-2 inhibitors with marked reduction in osteoblastogenesis histologically[37]. Etodolac, another COX-2 inhibitor, when given intraperitoneally daily for 3 weeks inhibited closed, non-displaced fractures in rats[38]. Animal data suggested that the effect of COX-2 inhibitors is both dose dependent and reversible[39]. On the other hand, celecoxib did not delay healing of right femurs in rats, as seen at 12 weeks postfracture. However, it increased fibrous healing at 4 and 8 weeks following fracture[31]. Gerstenfeld et al[27] reported that daily administration of ketorolac (a non-selective NSAID) had a greater effect on the process of healing compared with the

COX-2 selective NSAID; parecoxib (a prodrug of valdecoxib) which produced only a small effect[27].

Oxicams

Although heterotopic bone formation in quadriceps of the right hind limb in rabbits is inhibited by indomethacin; piroxicam seems to be ineffective[35]. However, tenoxicam given i.m. for a week before and 48 hours after fracturing rat tibia, delayed fracture healing[40].

Phenylbutazone

Phenylbutazone decreased healing rate of cortical defects in tibia when given orally to horses[41].

Effect of opioids and related compounds on fracture healing

Opioids peptides (selective agonist of some opioid receptors) accelerated the development of newly synthesized spongy bone tissue in mice when injected intraperitoneally within seven days postfracture[42]. Tramadol had no negative effect on the proliferation of human osteoblast in vitro[26].

Antibiotics

Fluoroquinolones, such as ciprofloxacin, have adverse effect on growing cartilage and endochondral ossification in children. Ciprofloxacin treatment for 3 weeks of rats with closed, non-displaced, bilateral femoral fracture beginning 7 days after fracture resulted in inhibition of healing during the early stages of fracture repair[43]. Levofloxacin and trovafloxacin diminished healing of experimental closed, non-displaced bilateral femoral fractures of rats, when given twice daily for 3 weeks beginning 7 days after fracture[44].

Gentamicin i.m. twice daily for 3 weeks did not cause impairment of healing of experimental fracture in male rats evaluated by radiological and torsional strength testing of fracture callus[45].

Vancomycin, administered intraperitoneally twice daily for three weeks did not impair healing of experimental fracture in rats[45].

Cefazolin-treated rats with closed, non-displaced, bilateral femoral fracture were not different from control[43].

Vitamins

Vitamin C

Vitamin C seems to be an essential substance in fracture healing. Single high dose of vitamin C intramuscularly accelerated healing of fractured right tibias in rats compared with control[46]. It also accelerated healing of right tibias in rats when administered 3 days before and 3 times per week for 21 days after fracture[47].

Vitamin E

Healing of fractured left fibulas of rabbits became better after administration of vitamin E (20mg/kg/day) intramuscularly for 5 days when assessed histologically at 4 weeks after facture[48]. Similar findings were obtained when right femur of rabbits were fractured in another experiment[49]. These effects are related to the antioxidant effect of vitamin E on oxygen radicals in the fractured area. Vitamin E also had positive effect on both early and late phase of fracture healing in rat tibia when administered intraperitoneally (20mg/kg). In this experiment, malondialdehyde concentrations, a measure of

lipid peroxidation associated with oxygen free radicals, were significantly decreased on day 15 and 45 days after fracture[50].

Vitamin D

Single high dose of vitamin D (chole-calciferol) intramuscularly (50000 IU/kg) stimulated fracture healing in right tibia of guinea pigs[51]. Similarly, calcidiol (25-OH-vit.D) administered subcutaneously to elderly female rats significantly improved the mechanical strength of fractures of middle third of both femora in rats 5 weeks later[52].

Hormones and local factors

Corticosteroids

Systemic corticosteroids (0.15mg/kg/day prednisolone) inhibited bone healing of ulnar osteotomy in rabbits[53]. Prednisolone given subcutaneously for 2 months before and 6 weeks after ulnar osteotomies performed in adult female rabbit clearly inhibited bone healing[54]. In contrast, methylprednisolone did not inhibit healing of intramedullary pinned osteotomies of femurs in rats 6 weeks after surgery[55].

Parathyroid hormone

Intermittent parathyroid hormone (200ug /kg/day for 20-40 days) increased callus formation and mechanical strength of the healing rat tibial fractures[56]. Recombinant human parathyroid hormone given to overiectomized rats once daily for 30 consecutive days during fracture healing of bilateral tibial shaft fractures, increased morphometric and mechanical parameters of the healing process[57]. Subcutaneous injection of low-dose parathyroid hormone (10μg/kg)enhanced healing of unilateral femoral fractures in rats evaluated 28 and 42 days after fracture[58].

Finally, parathyroid hormone injected subcutaneously into rats for 8 and 16 weeks can enhanced fracture strength and callus amount and after withdrawal, these parameters continued to increase[59].

Growth hormone

Growth hormone (given subcutaneously twice daily for 20 days) had an initially stimulatory effect on external callus formation in rats with closed tibial fracture and medullary nailing. However, the callus formed was loosely structured and was not removed by the normal modeling and remodeling process[60]. In addition, growth hormone stimulated massive invasion of marrow cells in the external fracture callus[60].

Estrogen and related compounds

In overiectomized rats, inhibitors of bone resorption (estrogen, raloxifene and alendronate) affect bilateral osteotomies of femoral midshafts fixed with intra-medullary wires differently. Alendronate markedly suppressed bone resorption and formation activity, while estrogen and raloxifene had insignificant effect on fracture repair[61]. Similarly, 17-beta-estra-diol did not offer advantage in terms of healing of bilateral shaft fractures in overiectomized rats[57].

Insulin

Deficiency of insulin had been reported to impair fracture healing in animal models of fracture[62].

Fibroblast growth factor-2(FGF-2)

This factor mixed with gelatin hydrogel was injected to each osteotomy site of rabbit proximal tibia. FGF-2 local application was found to have an

accelerating effect on the repair of meta-physeal fractures[63].

Nicotine

Systemic nicotine administration resulted in a significant lag in formation of cortical continuity of white rabbits with midshaft tibial osteotomies[64], 13% of fractures showed no clinical evidence of union in the nicotine group while all fractures in the control group healed. Biochemical testing showed the nicotine exposed bones to be 26% weaker in three-point bending test[64]. In rats, nicotine administration orally in drinking water, also impaired bone healing of parietal bone defects and grafting. is study reported previous in vitro data confirming that nicotine diminishes osteoblast function[65].

Alcohol

Ethanol (15%) given for 5 weeks to rats with tibial fractures fixed with intramedullary nails, was found to disturb bone metabolism; significantly lowering the body bone mineral density and total calcium than control[66].Moreover, ethanol reduced bending movement and bending stiffness both in fractured and unfractured tibiae. However, the healing process of an induced tibial shaft fracture was not affected[66]. Chronic ethanol consumption (for 6 weeks) of male rats, as part of liquid diet, resulted in deficient bone repair of an injury induced in both fibulae (evaluated through determining rigidity of the fibulae by three-point bending, and flexural modulus and mineral content of the repair tissue)[67].

Miscellaneous drugs

Cytotoxic drugs

Doxorubicin given intravenously as a single daily dose starting from the time of surgery (posterolateral lumber spinal fusion in rabbits) played a significant inhibitory role in the process of spinal fusion[68].

Statins

Statins were found to have anabolic effect on bone. Simvastatin included in the diet (~120 mg /kg body weight / day) was shown to increase callus transverse area of fractured femur of mice examined 14 days after fracture. The force required to break the bone and energy uptake were also increased[69].

Phenytoin

Phenytoin (intraperitoneally or locally in the fracture site) promoted healing of both radius of each rabbit; 9,16 and 30 days postfracture[70].In human, Tang et al[71] found that administration of phenytoin orally can markedly promote healing closed fractures of tibia and fibula.

Calciofix (a drug containing essential amino acids and lactose). This drug significantly accelerated rate of bone formation in transversal fractures of the left fibula and right femoral condyle defects in rabbits[72].

Drugs	Augmenting	Delaying	No effect
Prostaglandin	PGE_2 [15-18]		
NSAIDs		Aspirin[22,23] Diclofenac[22-26] Ketorolac[27] Ibuprofen[28,29] Naproxen[19,20] Indomethacin[16, 22,30-36] **COX-2 inhibitors**[19,27,31,37-39] Tenoxicam[40] Phenylbutazone[41]	Piroxicam[35]
Opioids	Opioid peptides[42]		Tramadol[26]
Antibiotics		Ciprofloxacin[43] Levofloxacin and trovafloxacin[44]	Gentamicin[45] Vancomycin[45] Cefazolin[43]
Vitamins	Vitamin C[46,47] Vitamin E[48,49,50] Vitamin D[51,52]		
Hormones	Parathyroid hormone[56-59] Growth factor[60] Insulin[62] Fibroblast growth factor-2 (FGF-2)[63]	Corticosteroids (prednisolone)[53,54] Alendronate[61] Estrogen[61] Raloxifene[61] 17-beta-estradiol[57]	Methylpredni-solone[55]
Nicotine		Nicotine[64, 65]	
Alcohol		Ethanol[66,67]	
Miscellaneous	Simvastatin[69] Phenytoin[70,71] Calciofix[72]	Doxorubicin[68]	

Table: Effects of different pharmacological agents in fracture healing.

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