

An Overview of Drug Effects on Bone Healing on Animal Research Models

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Abstract

Bone fracture is a common health problem in humans and animals, and the healing of the bone fracture is a complicated process. Several drugs may be used concurrently with the treatment of fractures, but they may interfere with the healing process of the bone. The present research reviewed previously published studies with the objective to enhance the understandings of the effects of different drugs on bone healing. There is clear evidence that antibiotics, corticosteroids, non-steroidal inflammatory drugs, and chemotherapeutic drugs all affect bone healing. By contrast, the effect of anticoagulants on bone healing is controversial, so more research is needed to determine its efficacy. In addition, there is no direct evidence to approve the effect of anesthetics on bone healing, so this is another area in need of further research.

Keywords

Animal model, bone healing, drug, rat femur

Introduction

Bone fracture causes harmful effects to patients' health, degrades their quality of life, and is responsible for costly treatments. Annually, millions of musculoskeletal procedures are performed worldwide (Jahangir *et al.*, 2008). Each year, billions of dollars have been spent for the treatments of bone fracture and hip replacement, and the number has been increasing over time. In 2005, more than USD 20 billion was spent on medical care for over 300,000 spinal fusions (Porter *et al.*, 2009). Pathogenic bone defects caused by cancer were responsible for more than 3,000 pediatric hospitalizations, and cost over USD 70 million (Porter *et al.*, 2009).

In animals, about 800,000 pets are involved in vehicle crashes annually in USA (Strickland, 2014). High rise syndrome may cause limb fracture in 46.2% of fallen cats, of which 38.5% of fractures are in forelimbs and 61.5% were in the hind limbs are. Tibiae are most commonly fractured followed by the femur (Vnuk *et al.*, 2004). The treatment cost of bone fractures in companion animals can procure

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several million Vietnam Dong per case.

Antibiotics, anti-inflammatory drugs and anesthetics are usually used during treatment of bone fracture. Sometimes, anticoagulants or chemotherapy drugs may be applied in orthopaedic animals treatments. All of these drugs may have some effects on the course of bone healing. The pharmacological factors associated with bone healing in humans and animals are similar in many aspects; therefore, understanding these factors is useful and can enhance the successful treatment. This narrative review focuses on the effects of drugs used on the bone healing process based on the information retrieved from an extensive literature review.

Effects of Drugs on Bone Healing

Prevention and/or treatment of diseases may involve many types of drugs. They can be generally divided into 6 groups including antibiotics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, chemotherapeutic agents and anesthetics. When used in animals with bone fractures, some of these drugs may interfere with the bone healing process. **Tables 1-5** present the effects of such drugs on fracture healing in animal models.

Effects of Antibiotics on Bone Healing

Many antibiotics have been reported to affect bone healing including quinolones (Gough *et al.*, 1996), ciprofloxacin (Huddleston *et al.*, 2000), levofloxacin and trovafloxacin (Perry *et al.*, 2003), tetracycline (Kim *et al.*, 2004) and cefuroxime (Natividad-Pedreño *et al.*, 2016). Effect of gentamicin on bone healing is controversial. Kim *et al.* (2004) reported that it decreased bone formation, however, Fassbender *et al.* (2013) and Haleem *et al.* (2004) did not find similar results. Cefazolin had no effect on fracture healing parameters including callus mechanical resistance and histological scores (Natividad-Pedreño *et al.*, 2016). Also, vancomycin did not influence biomechanical and radiographic scores of healing bone (Haleem *et al.*, 2004). Interestingly, doxycycline inhibited osteolysis, and is suggested for prevention and

treatment of wear particle-induced osteolysis and aseptic loosening (Zhang *et al.*, 2007).

The negative effects of antibiotics on bone healing may be due to their high doses such as 100 mg/kg/day for cefuroxime (Natividad-Pedreño *et al.*, 2016) and ciprofloxacin (Huddleston *et al.*, 2000), 70 mg/kg/day for trovafloxacin and 50 mg/kg/day for levofloxacin (Perry *et al.*, 2003), and due to long treatment durations, such as 3-4 weeks (Huddleston *et al.*, 2000; Perry *et al.*, 2003; Natividad-Pedreño *et al.*, 2016). Antibiotics play a pivotal role in prevention and treatment of bacterial infection in many diseases and procedures, especially, orthopedic cases. The use of antibiotics is inevitable as long as their doses and durations are carefully calculated and followed.

Effects of corticosteroids on Bone Healing

In vivo studies have demonstrated that many corticosteroids including cortisone (Sissons & Hadfield, 1955), prednisolone (Luppen *et al.*, 2002; Yaghini *et al.*, 2017), prednisone (Bostrom *et al.*, 2000; Waters *et al.*, 2000), methylprednisolone (Xie *et al.*, 2011) and dexamethasone (Sawin *et al.*, 2001) affected the bone healing process. The common aspect of these studies was that the duration of treatments was prolonged, i.e., 42 days for dexamethasone (Sawin *et al.*, 2001), 56-78 days for prednisolone (Luppen *et al.*, 2002; Yaghini *et al.*, 2017) and 96 days for prednisone (Bostrom *et al.*, 2000; Waters *et al.*, 2000). On the other hand, when used for a shorter duration, i.e., 14-21 days, corticosteroid doses were very high, i.e., 20mg/kg/day for methylprednisolone (Xie *et al.*, 2011), and 10-20 mg/kg/day for cortisone (Sissons & Hadfield, 1955). With a similar duration of treatment (21 days) but several times lower doses (0.5 mg/kg/day), no significant effect of prednisolone on fracture healing was observed although the numeric values of the mechanical parameters were lower in the treated group (Bissinger *et al.*, 2016). Being used for 4 consecutive days, methylprednisolone at 2 mg/kg/day (Hogevold *et al.*, 1992) and prednisone at 0.02 mg/kg/day (Aslan *et al.*, 2005) had no effect on bone healing.

Table 1. *In vivo* effects of different antibiotics on bone healing

Drug and dosage	Animal and bone	Results	References
Cefazolin: 50 mg/kg per day, daily for 4 weeks. Cefuroxime: 100 mg/kg per day, daily for 4 weeks.	Rat femur	Cefuroxime decreased callus mechanical resistance and lowered histological grade. Cefazolin did not influence studied parameters.	Natividad-Pedreno <i>et al.</i> (2016)
Gentamicin: 10% gentamicin coated implant.	Rat tibia	Local application of gentamicin did not influence tibial fracture healing.	Fassbender <i>et al.</i> (2013)
Doxycycline: 2 and 10 mg/kg per day for 7 days.	Mouse calvaria	Doxycycline inhibited osteolysis. Suggestion for use of doxycycline for treatment or prevention of wear particle-induced osteolysis and aseptic loosening.	Zhang <i>et al.</i> (2007)
Tetracycline: 30 mg/graft. Gentamicin: 15 mg/graft.	Rat calvaria	Antibiotics impaired bone formation.	Kim <i>et al.</i> (2004)
Gentamicin: 1.5 mg/kg, twice per day for 3 weeks. Vancomycin: 25 mg/kg, twice per day for 3 weeks.	Rat calvaria	Antibiotics had no effects on biomechanical and radiographic scores.	Haleem <i>et al.</i> (2004)
Levofloxacin: 25 mg/kg, trovafloxacin: 35 mg/kg. Both drugs were used twice a day for 3 weeks, started 1 week post femoral fracture.	Rat femur	Antibiotic induced less woven bone and more cartilage in the fracture sites.	Perry <i>et al.</i> (2003)
Ciprofloxacin: 50 mg/kg, twice a day for 3 weeks, 1 week post femoral fracture.	Rat femur	Decreased radiographic results, lowered torsional strength, and abnormal cartilage morphology were observed in the treatment group.	Huddleston <i>et al.</i> (2000)
Quinolones: 100, 350, 500, 750 mg/kg per day for 5 days.	Rabbit joints: shoulder, hip, knee	Drug caused degenerated or hypertrophic chondrocytes, loss of collagen and proteoglycan. Effects were not clearly dose-related.	Gough <i>et al.</i> (1996)

The negative effect of corticosteroids on bone healing was consistent in the literature, especially if the high doses and/or long treatments were applied. Nonetheless, there is also some evidence that corticosteroids can be used for a short time with appropriate doses if their benefits outweigh their potential side effects.

Effects of non-steroidal anti-inflammatory drugs on Bone Healing

The inhibitory effect on bone fracture healing is attributable to many NSAIDs, including indomethacin (Brown *et al.*, 2004; Hogevoid *et al.*, 1992; Lack *et al.*, 2013), ketorolac (Gerstenfeld *et al.*, 2003), etodolac

(Endo *et al.*, 2002), diclofenac (Bissinger *et al.*, 2016; Krischak *et al.*, 2007), ibuprofen (Kidd *et al.*, 2013; Leonelli *et al.*, 2006), dexketoprofen and meloxicam (Inal *et al.*, 2014), aspirin (Lack *et al.*, 2013), parecoxib (Gerstenfeld *et al.*, 2003), rofecoxib (Leonelli *et al.*, 2006) and celecoxib (Simon & O'Connor, 2007). Most of these NSAIDs doses were below or comparable to the recommended dosage for treatment of diseases in humans. Only some of these studies used high doses of NSAIDs, i.e., indomethacin at 12.5 mg/kg/day, aspirin at 100-300 mg/kg/day (Lack *et al.*, 2013), and rofecoxib at 8 mg/kg/day (Leonelli *et al.*, 2006). Impaired fracture healing may be partially due to long-term exposure to drugs, including diclofenac for 21 days (Bissinger *et al.*, 2016), rofecoxib and ibuprofen

Table 2. *In vivo* effects of corticosteroids on bone healing

Drug and dosage	Animal and bone	Results	References
Prednisolone: 4 mg/day for 4 weeks, followed by 2 mg/day for another 4 weeks.	Dog mandible	Prednisolone decreased bone-implant contact.	Yaghini <i>et al.</i> (2017)
Prednisolone: 0.5 mg/kg per day, daily for 21 days.	Rat femur	No significant effect of prednisolone on bone healing was evident although the absolute values of mechanical parameters in prednisolone group were lower in comparison with the control.	Bissinger <i>et al.</i> (2016)
Methylprednisolone: 20 mg/kg per day, three times on day 16, 15 and 14 pre-surgery.	Rabbit femur	Methylprednisolone induced osteonecrosis, impaired healing and maturation of bone tissue.	Xie <i>et al.</i> (2011)
Prednisone: 0.02 mg/kg, 4 consecutive days started prior to surgery.	Rat femur	Prednisone had no effect on bone healing.	Aslan <i>et al.</i> (2005)
Prednisolone: 0.35 mg/kg per day, three times a week for 6 weeks before surgery.	Rabbit ulna	Prednisolone inhibited bone healing characterized by a small callus area, low torsional strength.	Luppen <i>et al.</i> (2002)
Dexamethasone: 0.05 mg/kg per time, twice every day for 42 days since surgery.	Rabbit spine	Dexamethasone decreased the rate of bone graft union.	Sawin <i>et al.</i> (2001)
Prednisone: 0.15 mg/kg per day, 60 days before osteotomy until 6 weeks postosteotomy.	Rabbit ulna	Prednisone induced bone loss.	Bostrom <i>et al.</i> (2000)
Prednisone: 0.15 mg/kg per day, 60 days before osteotomy to 6 weeks post-surgery.	Rabbit ulna	Prednisone caused lower results in callus size, radiographic density, bone mineral content and mechanical strength.	Waters <i>et al.</i> (2000)
Methylprednisolone: 2 mg/kg, 4 consecutive days started prior to surgery.	Rat femur	Methylprednisolone had no inhibitory effect on bone healing.	Hogevold <i>et al.</i> (1992)
Cortisone: 10, 20 mg/kg per day for 14 days.	Rabbit femur and tibia	Longitudinal bone growth instantly stopped after the commencement of cortisone administration. The cartilage was thinned as soon as day 6. By day 24 extensive destruction of metaphyseal trabeculae was apparent.	Sissons & Hadfield (1955)
Cortisone: 20 mg/kg per day for 21 days.	Rat femur and tibia	The harmful effect of cortisone on bone growth in rats was less severe than in rabbits.	

for 28 days (Leonelli *et al.*, 2006), ketorolac and parecoxib for 35 days (Gerstenfeld *et al.*, 2003), indomethacin, celecoxib for 28, 56 or 112 days (Brown *et al.*, 2004). The inhibitory effect of NSAIDs on fracture healing was observed even when the treatment durations and doses were

comparable to ordinary prescription, ie., indomethacin at a dose of 2 mg/kg/day for 4 days (Hogevold *et al.*, 1992), etodolac at 20 mg/kg/day for 7 days (Endo *et al.*, 2002) and celecoxib at 4 mg/kg/day for 5 days (Simon & O'Connor, 2007).

Although there are a few studies supporting the use of some NSAIDs, such as ketorolac (Cappello *et al.*, 2013; Fracon *et al.*, 2010), paracetamol, etoricoxib (Fracon *et al.*, 2010) during bone healing treatment, there are far more studies reporting the newgative impact of bone healing. Therefore, use of NSAIDs during fracture healing should only be considered when the drugs' benefits over-ride their negative impacts (**Table 3**).

Effects of anticoagulants on Bone Healing

The use of anticoagulants for prevention of thrombosis and pulmonary embolism in traumatic and orthopedic cases is common (Prodinger *et al.*, 2016). Anticoagulants may elicit inhibitory effects on osteoblast formation, and may intensify bone resorption (Kapetanakis *et al.*, 2015). Enoxaparin has been found to exert a negative effect on fracture healing in rabbit ribs (Street *et al.*, 2000, whereas this drug does not influence bone healing of rat femur (Curcelli *et al.*, 2005; Demirtas *et al.*, 2013; Say *et al.*, 2013). Bone fracture healing is independent of many anticoagulants, including heparin (Curcelli *et al.*, 2005; Erli *et al.*, 2006), dalteparin (Erli *et al.*, 2006; Hak *et al.*, 2006; Say *et al.*, 2013), certoparin (Erli *et al.*, 2006), nadroparin (Say *et al.*, 2013), and rivaroxaban (Demirtas *et al.*, 2013). Rivaroxaban increased the callus volume

but decreased bone mineral density resulting in unchanged mechanical parameters (Kluter *et al.*, 2015; Prodinger *et al.*, 2016). It appears that negative effects of anticoagulants on bone fracture healing is still minimal. A definitive conclusion of the effect of anticoagulants on bone healing is impossible discern due to the differences in drugs used, time of drug exposure, drug doses, animal models, fractured bones, time of evaluation and means of evaluation. Therefore, these drugs are still a gold standard for prevention of thrombosis and pulmonary embolism in animals with bone fracture(s). Nevertheless, more well-designed studies are required to determine the true effects of anticoagulants on bone fracture healing (**Table 4**).

Effects of chemotherapeutic agents on Bone Healing

Chemotherapeutic agents are commonly prescribed for treatment of cancers and chronic inflammation. High doses are recommended for oncological treatment, and low doses are for chronic inflammation (Cavalcanti *et al.*, 2014). Results show that these drugs are also significantly involved in the bone healing process. Fracture healing was completely prevented by angiogenesis inhibitor TNP-470 via suppression of both intramembranous and endochondral ossifications (Hausman *et al.*, 2001). Histological and radiographical

Table 3. *In vivo* effects of NSAIDs on bone healing

Drug and dosage	Animal and bone	Results	References
Diclofenac: 5 mg/kg per day for 21 days.	Rat femur	Diclofenac decreased stiffness, trabecular thickness and callus volume.	Bissinger <i>et al.</i> (2016)
Dexketoprofen: 0.98 mg/kg per half a day, meloxicam: 0.2 mg/kg per day, diclofenac: 1mg/kg per day. All drugs were used for 10 days.	Rat fibula	Dexketoprofen and meloxicam inhibited bone fracture healing while diclofenac did not.	Inal <i>et al.</i> (2014)
Indomethacin: 12.5 mg/kg per day. Aspirin: 2.7 mg/kg per day, 10 mg/kg per day, 50 mg/kg twice per day, 100 mg/kg three times per day. All drugs were used for 8 weeks.	Rabbit ulna	Aspirin at 10 mg/kg and 100 mg/kg, and indomethacin decreased bone healing.	Lack <i>et al.</i> (2013)

Drug and dosage	Animal and bone	Results	References
Ketorolac: 5 mg/kg per day for either 7, 14 or 21 days.	Rat tibia	No effect of ketorolac on bone healing was seen at any time point of evaluation.	Cappello <i>et al.</i> (2013)
Ibuprofen: 30 mg/kg per day for either 2, 4, or 6 weeks.	Rat ulna	Treatment of ibuprofen decreased bone resorption and reduced bone formation which resulted in lower length and area of lamellar bone.	Kidd <i>et al.</i> (2013)
Paracetamol: 80 mg/kg per day. Ketorolac: 4 mg/kg per day. Etoricoxib: 10 mg/kg per day. All drugs were daily used, for 2 weeks since surgery.	Rat tooth socket	No drug had an inhibitory effect on volume fraction of trabecular bone.	Fracon <i>et al.</i> (2010)
Diclofenac: 5 mg/kg per day for either 7 or 21 days.	Wistar rats	Histomorphometric evaluation revealed that long-term instead of short-term treatment of diclofenac resulted in a higher amount of cartilage and less bone.	Krischak <i>et al.</i> (2007)
Celecoxib: 2, 4, 8 mg/kg per day for 15 days, started 4h post fracture. 4 mg/kg per day for either 5, 10, 21, or 28 days started 4h postfracture. 4 mg/kg per day, started at 5 days prefracture, or 1, 7, 14 days postfracture, until day 28.	Rat tibia	Use of celecoxib for 15 days at any studied doses increased the rate of bone nonunion. A dose of 4 mg/kg for 5 days decreased the mechanical strength and increased the nonunion rate. No harmful effect was detected when the use of celecoxib was commenced at 5 th day prior to or at 14 th day after operation.	Simon & O'Connor (2007)
Rofecoxib: 8 mg/kg per day for 4 weeks. Ibuprofen: 30 mg/kg per day for 4 weeks.	Rat femur	Incidence of nonunion in rofecoxib and ibuprofen groups was higher than that in the control group.	Leonelli <i>et al.</i> (2006)
Indomethacin: 1 mg/kg per day for 4,8,12 weeks. Celecoxib: 3 mg/kg per day for 4,8,12 weeks.	Rat femur	Both indomethacin and celecoxib delayed bone healing at 4 and 8 weeks post operation.	Brown <i>et al.</i> (2004)
Ketorolac: 4 mg/kg per day, for either 21 or 35 days. Parecoxib: 0.3 and 1.5 mg/kg per day for either 21 or 35 days.	Rat femur	Both parecoxib and ketorolac impaired bone healing, but ketorolac expressed more harmful effects.	Gerstenfeld <i>et al.</i> (2003)
Etodolac: 20 mg/kg per day for 3 weeks started from surgery until day 21, or for 1 week started from surgery until day 7, or for 1 week started from day 14 until day 21.	Rat femur	In all groups of treatment, radiographic and mechanical testing showed lower scores which predisposed fractures to delayed healing.	Endo <i>et al.</i> (2002)
Indomethacin: 2 mg/kg, 4 consecutive days started prior to surgery.	Rat femur	Indomethacin impaired bone healing. This effect was more severe when fracture healed under unstable condition.	Hogevold <i>et al.</i> (1992)

assessments revealed that doxorubicin and cisplatin affect both quantity and quality of the healing bone of rabbit segmental radial diaphyseal fractures (Morcuende *et al.*, 2004). Even a single dose of doxorubicin at the time of surgery significantly inhibited the process of spinal fusion (Tortolani *et al.*, 2004). Similarly, a single dose of methotrexate at either 30 or 250mg at surgery decreases bone formation resulting in impaired bone healing (Cavalcanti *et al.*, 2014; Satoh *et al.*, 2011). By contrast, methotrexate at a low dose (3mg every week, for 1-4 weeks) did

not delay fracture healing process (Cavalcanti *et al.*, 2014; Satoh *et al.*, 2011). The effect of chemotherapeutic agents on bone healing may depend on drug types, and the doses of drugs. Although the effects of chemotherapeutic agents on bone healing are apparent, their use in some cases, including cancer, can not be avoided. In such cases, adjunctive treatment such as growth factors may be considered to reduce the drugs' negative effects and normalize bone healing process (**Table 5**).

Table 4. *In vivo* effects of anticoagulants on bone healing

Drug and dosage	Animal and bone	Results	References
Rivaroxaban: 600 ppm/g of medicated food, enoxaparin: 100 IU/kg twice every day for 21 days.	Rat femur	Rivaroxaban increased callus volume which corresponded to reduced bone density. Treatment of both rivaroxaban and enoxaparin resulted in enlarged callus surface, trabecular thickness, and degree of bone anisotropy. Biomechanical characteristics were not influenced by any drugs administered.	Prodingner <i>et al.</i> (2016)
Rivaroxaban: 3 mg/kg per day for either 28 or 49 days.	Rat femur	Rivaroxaban increased callus volume and induced a marginal increase in bone mineral density, but torsional rigidity was not affected by the treatment.	Klüter <i>et al.</i> (2015)
Enoxaparin: 1000 anti Xa IU/kg per day, rivaroxaban: 3 mg/kg per day, fondaparinux: 0.2 mg/kg per day for 21 days.	Rat femur	No effects of enoxaparin, rivaroxaban and fondaparinux on fracture healing was noticed via radiographic and histopathological examinations.	Demirtas <i>et al.</i> (2013)
Fondaparinux: 1 mg/kg per day, dalteparin: 140 µg/kg per day, nadroparin: 200 µg/kg per day, enoxaparin: 1 mg/kg per day for 28 days.	Rat femur	Fondaparinux had a stimulatory effect on bone healing. Dalteparin, nadroparin, and enoxaparin had no effect on fracture healing.	Say <i>et al.</i> (2013)
Heparin: 133 IE/kg per day, certoparin: 50 anti-Xa-units/kg per day, dalteparin: 50 anti-Xa-units/kg per day for 42 days.	Rabbit femur	Histological examination revealed that there was no significant effect of anticoagulants on bone healing.	Erli <i>et al.</i> (2006)
Dalteparin: 70 unit/kg per day for 14 days.	Rat femur	Dalteparin did not alter radiographic, histological and, mechanical results.	Hak <i>et al.</i> (2006)
Heparin: 400 IU/kg per day, enoxaparin: 2 mg/kg per day for 28 days.	Rat femur	Heparin and enoxaparin had no effect on histological and mechanical grades.	Curcelli <i>et al.</i> (2005)
Enoxaparin: 2 mg/kg per day for either 3, 7, 14, or 21 days.	Rabbit rib	Inhibitory effect of enoxaparin on bone healing was detected at all times of evaluation.	Street <i>et al.</i> (2000)

Table 5. *In vivo* effects of chemotherapeutic agents on bone healing

Drug and dosage	Animal and bone	Results	References
Methotrexate: 3 mg per week for 1, 2, 4 weeks or a single dose of 30 mg/kg.	Rat mandible	High dose of methotrexate impaired bone healing characterized by decreased bone formation.	Cavalcanti <i>et al.</i> (2014)
Methotrexate: High dose: 250 mg/kg on the day of surgery. Low dose: 3 mg/kg per week for 4 weeks before surgery until either 1 or 4 weeks after surgery.	Rat femur	High dose rather than low dose of methotrexate significantly impaired bone healing.	Sato <i>et al.</i> (2011)
Doxorubicin: 2.5 mg/kg at surgery.	Rabbit spine	Bone fusion rate was reduced in the treatment group.	Tortolani <i>et al.</i> (2004)
2.5 mg/kg of both doxorubicin and cisplatin three times, i.e. at 4 days prior to 7 and 14 days after operation.	Rabbit radius	Chemotherapy decreased bone area and bone density.	Morcuende <i>et al.</i> (2004)
Angiogenesis inhibitor TNP-470: 30 mg/kg per day, every other day for either 7, 14, or 21 days.	Rat femur	Antiangiogenic drug prevented bone formation.	Hausman <i>et al.</i> (2001)

Effects of Anesthetics on Bone Healing

Anesthetics are routinely utilized in many surgical procedures, particularly in orthopedics. Besides their anesthetic properties, they also have anti-inflammatory characteristics. Isoflurane reduces the systemic release of TNF- α and IL-1 β (Flondor *et al.*, 2008). TNF- α , IL-6 and IL-8 production from human whole blood culture was also suppressed by ketamine (Kawasaki *et al.*, 1999). Furthermore, ketamine lowers TNF- α activity and mortality of carrageenan-sensitized endotoxemic rats (Koga *et al.*, 1994), and decreases TNF- α production in LPS-induced endotoxemia in mice (Taniguchi *et al.*, 2001). Interestingly, ketamine did not exert those effects if endotoxins were absent. The mechanism of ketamine-induced anti-inflammation is believed to be partially due to its effect on cyclooxygenase activity (Suliburk *et al.*, 2005). Furthermore, in rats, the anti-inflammatory effect of ketamine was seen only at sub-anesthetic dosages (0.5-5 mg/kg), whereas at high dosage (50 mg/kg) it enhanced the TNF- α production (Sun *et al.*, 2004). Although there are no direct results showing that anesthetics influence bone fracture healing, their effects on

inflammatory cytokines are apparent. The bone healing process is, on the other hand, involved in the inflammatory mechanism. Therefore, it may be hypothesized that some anesthetics such as isoflurane and ketamine may influence bone fracture healing (Histing *et al.*, 2011). Because the true effect of anesthetics on bone healing has not been determined to date, their use still contributes to the success of millions of orthopedics procedures worldwide.

Conclusions

This overview showed that the course of bone healing may be influenced by several drugs and treatment regimes. However, the negative effects of several antibiotics and steroids on bone healing may be due to their high doses and/or long treatments because such effects were absent when normal doses and treatment periods were applied. The use of such drugs in patients with bone fracture(s) is reasonable if the normal doses and durations of treatments are followed. In contrast, many non-steroidal inflammatory drugs may affect bone healing even at their standard treatment usage. Hence, these drugs should not

be prescribed for orthopedic animals treatments. There is a large body of research demonstrating negative effects of chemotherapy agents on bone healing. However, a low dose of methotrexate may be appropriate for animals that have cancer or chronic inflammation and acquire bone fracture(s). More well-designed studies are needed before a conclusion on the effect of anticoagulants and anesthetics on bone healing process can be ascertained. The use of some drugs is inevitable during the treatment of bone fractures, therefore, understandings of their effects on bone healing are imperative to increase the chances of successful treatments.

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