Efficacious Single-Dose Multimodal Long Acting Parenteral and Local Analgesia for Femur Fracture and Sciatic Nerve Injury in Rat Model

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Introduction

Femur fractures and sciatic nerve injury produce severe pain in laboratory animals involved in medical research. An effective pain management regimen is critical for relieving pain and facilitating positive outcomes of research studies. Opioid analgesics are the gold standard for relieving pain in invasive procedures including orthopedic, thoracic, and other surgeries [1]. However, nausea associated with opioid use can be deleterious especially in rats which are physically incapable of vomiting placing them at risk for gastric distention, pica, malnutrition, weight loss, and death [2]. Opioid-induced neuropathic pain, particularly when given in repeated intervals, is also a major complication [3, 4]. An analgesic protocol in laboratory animals utilizing a multimodal approach that incorporates analgesics from various classes such as opioids, nonsteroidal anti-inflammatory drugs (NSAID) [5], preoperative and intraoperative analgesia; and the use of local anesthetic agents to block nociceptive signaling (e.g., bupivacaine) could help reduce the need for opioid analgesics and prevent side effects [6]. We present here results of a preliminary study that demonstrates benefits of using a multimodal approach of long acting analgesic drugs for pain management in laboratory rats. Thirty-eight (38) rats with concomitant femur fracture and sciatic nerve injury demonstrated satisfactory pain management within 3 days of operation using a single dose of peripherally Buprenorphine-SR, Meloxicam-SR, and local Bupivacaine-SR while receiving palatable food (7).

Method

Thirty-eight rats (Sprague Dawley®, male, 300 grams, Charles River) were divided into 3 groups: a cast group, an open reduction and internal fixation (ORIF) group, and a non-operative placebo surgery group. The rats were anesthetized with isoflurane (4% induction, 2% maintenance), weighed to determine the dosage of peripherally acting Buprenorphine-SR and Meloxicam-SR subcutaneously (1.2 mg/kg) and Meloxicam SR subcutaneously (4 mg/kg). The rats were placed on a warming pad maintained at 40°C. Ceilums, their eyes were covered with an ophthalmic lubricant, and their hair shaved around the incision site. The skin at the incision site was sterilized by washing with povidone and 70% alcohol three times before applying sterile drapes. The depth of anesthesia was ascertained by lack of pedal reflex to toe pinch. A 4 cm right posterolateral incision from lip to the ankle joint was made to expose the sciatic nerve (figure 1). Upon identification, isolation, and neurotomy of the cutaneous branch of the sciatic nerve, the nerve (5 mm proximal to the nerve entry point) was clamped with a hemostat for 10 seconds to induce a crush injury. The proximal zone of injury was tagged using an 8-0 nylon suture.

In addition to inducing sciatic nerve injury, the femur of each rat was completely fractured transversely at the level of the nerve injury using an electronically powered saw. If the rats were in the cast group, the wound was closed with skin clips and the rats administered a 5cc bolus of normal saline subcutaneously before application of a cast which was wrapped around the proximal right lower extremity. We improvisied a lighter cast (figure 2 B), to make it more comfortable for the animals. For rats that were assigned to the ORIF group, we plated the diaphyseal femur fracture laterally by using 4 screws (2 proximal and 2 distal) inserted at the fracture site. These rats also had their wounds closed with skin clips and were also administered a 5cc bolus of normal saline, subcutaneously. After the surgery was completed and the anesthesia stopped, 0.25% Bupivacaine was administered as a local anesthetic at a dosage of 2 mg/kg to the incision site and the rats were gently placed into a new cage with food, water, and a nutrient rich viscous paste, DietGel Boost Clear H2O. Westbrooks inc (4 ml) to facilitate their full recovery. The skin staples of all the rats were removed after approximately 14 days.

Conclusion

This observational study followed the progress of 38 rats undergoing multimodal pain treatment after concurrent femur fracture and sciatic nerve injury. Sufficient pain management within 3 days of the operation was achieved using a single dose of peripherally Buprenorphine-SR, Meloxicam SR, and the intraoperative local anesthetic Bupivacaine. The rats quickly regained mobility without signs of distress or pain and therefore did not require further pain medication. The results provided preliminary data of the benefits of using a multimodal pain management protocol (preemptive, neuraxial, opioid and SSAD), local anesthetic and palatable high energy food) to avoid the need for prolonged use of opioid analgesics drugs and preventing their associated side effects. Future studies are directed toward biochemical analysis to quantify levels of pain in rats and to extend the new pain management protocol to different strains of rats and animal species.

References

6. Guide for the Care and Use of Laboratory Animals. 8th ed., 2011, p121