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What's Next? Assessment of pain in rodents and practical analgesic strategies: improving postoperative well-being

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It is generally accepted that humans and animals alike experience pain with both a sensory and affective or emotional component. Evidently practitioners must rely on nonverbal assessments to score and treat pain where breakthrough pain occurs despite analgesic prophylaxis for procedures that are anticipated to lead to more than momentary pain or distress. As is common is prey species, rodents may mask pain or hide discomfort as this instinct is intrinsic in survival. Acute pain is identified using a number of established observations like guarding, vocalization, irritation at site, restlessness, depression, lethargy, or abnormal appearance. It is reasonable to believe that by the time these signs manifest that the nociceptive cascade is well underway and requires the practitioner to 'chase' the pain rather than preempt it. This may occur in the presence of insufficient preemptive analgesia or where breakthrough pain occurs due to individual variability.

New tools for pain assessment in rodents

A recent study published in Nature Methods[1] by investigators at McGill University was the first to translate assessments used in nonverbal patients (e.g. neonates and infants) to score and evaluate pain in rodents through the analysis of facial expression. This study attracted a tremendous amount of controversy with regard to conduct since, as is typical in pain research, a number of conventional assays designed to mimic pain states in humans were applied to animals without analgesia to study the response to pain. This unfortunately might have distracted from the rationale behind the study - to create a tool for finding new veterinary drugs that ease animal suffering and improving preclinical model fit in developing a powerful new approach for scoring analgesic efficacy. This relatively simple scale, termed the 'mouse grimace scale' (MGS), can present as an opportunity for investigators using rodents to add a new tool in assessing and treating pain. The study detected five signs indicative of pain in mice: the eyes close and tighten, nose and cheeks bulge, ears flatten and whisker position changes. Analgesic administration was effective in diminishing pain as measured by the MGS. As various groups begin to adopt the scale to attempt to identify and prevent subtle distress or recognize pain before more blatant symptoms manifest, there is potential for the MGS to serve as a highly relevant refinement.

Analgesic selection

All individuals who work with animals in biomedical research have a moral obligation to provide for the well-being of animals through the avoidance or minimization of discomfort, distress and pain in laboratory animals. One must administer analgesia to animals undergoing procedures that cause more than momentary or slight pain or distress. Analgesics reduce or relieve pain without loss of consciousness. When choosing an ideal post-surgical/procedural analgesic drug(s), one must take into consideration several factors included, but not limited to, the location, anticipated intensity and duration of post-surgical/post-procedural pain. Unless specifically contraindicated, analgesic administration should occur before/during the procedure to ensure efficacious levels are achieved prior to the animal recovering from anesthesia. This concept is referred to as pre-emptive analgesia. This is particularly important when animals are anesthetized with gas anesthetics (e.g. isoflurane) as the recovery is relatively quick and residual analgesia is minimal. Systemic and/or local analgesics may also reduce the anesthetic requirements, and also have a pre- emptive effect on pain perception that persists into the recovery period. The most commonly used systemic analgesics in laboratory animal species are opioids (e.g. morphine, buprenorphine, tramadol, etc) and Non-Steroidal Anti- Inflammatory Drugs or NSAIDs (e.g. Carprofen, meloxicam, etc). The ultimate decision for selection of drug must be based upon the species, intensity/duration of pain, and whether or not a specific analgesic may be contraindicated in the species of animal of have a confounding effect on the research data. To manage these scenarios, many veterinarians employ a multi-modal approach to pain management. The concept of multimodal analgesia involves the use of different classes of analgesics (systemic and local) and different sites of analgesic administration to provide superior dynamic pain relief with reduced analgesic-related side effects. This concept becomes a reality as new efficacy data is published and certain analgesic availability becomes variable. In light of recent and potential buprenorphine accessibility limitations we asked several of our ASR veterinarians to share with us their recommendations for rat analgesic protocols for post-operative pain relief in major operative procedures inclusive of thoracotomy, laparotomy, and orthopedic procedures. The following table represents a compilation of the options presented (including buprenorphine options):

Drug	**Dose**	**Frequency**
Buprenorphine	0.01-0.05mg/kg SC	BID-TID, q8-12hours
Oxymorphone	0.2-0.5mg/kg SC	q4h
Morphine	1-2.5mg/kg SC	q2-6h
Ketoprofen	2-5mg/kg SC	SID-BID
Carprofen	2-5mg/kg SC	SID-BID
Meloxicam	1-2mg/kg PO, SC	SID-BID
Flunixin	2.5mg/kg SC	SID
Local Infiltration*		
Lidocaine	10mg/kg	1-3 minutes onset
Bupivacaine	<6-8mg/kg	20 minute onset
* Note: Epinephrine prolongs action		

Effective pain management relies on thoughtful drug selection and attention to the following strategies: (1) assurance the selected preoperative analgesic is relevant to the intensity and procedure type or location; (2) performance of routine pain assessments; (3) treatment of pain as early as possible; (4) use of supportive measures in combination, e.g. warming pads, soft bedding, etc; (5) modification of the analgesic regimen to the individual response; (6) and provision of continuous analgesic coverage.

1. Langford DJ, Bailey AL, Chanda ML, Clarke SE, Drummond TE, et al. (2010) Coding of facial expressions of pain in the laboratory mouse. Nature Methods 7: 447–449.

Tech Tips

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Tips To Assist in Maintaining Non-human Primate (NHP) Body Temperature During Surgery

Like most species, non-human primates often require special attention to maintaining body temperature during anesthesia and surgery to prevent hypothermia. Our surgical team has made additional modifications to address this issue successfully! We would like to share our strategies in hopes that this may assist other surgical teams combat this concern.

Our first line of defense is the donning of a cap and socks. As soon as the NHP is placed on the surgery table we place a cap on its head and socks on its hands and feet. We use newborn size caps and various sized socks purchased from a local department store. These are quick and easy to apply and are very easy to clean and reuse.

Although some surgical tables are equipped with warming elements, ours are not. As you all know, a stainless steel surgical table can be very cold. We solved this problem by placing a warm-water circulating blanket under the NHP. On the morning of surgery, turning this blanket on is one of the first tasks on our list of things to do. This ensures that it is fully warmed when the NHP is placed on the table. If possible, we place a Bair Hugger warm air blanket over or around the NHP to insulate and further aid in maintaining body temperature.

The NHP is covered with surgical drapes for the surgical procedure, which also aids in maintaining body temperature. During the surgical procedure, we monitor the animal's body temperature constantly using the Surgivet Monitor with a sensor placed either orally or rectally depending on the surgical procedure. The temperature of the Bair Hugger blanket can then be adjusted, up or down, as needed to help maintain a constant body temperature, which ideally is 37.0 to 39.0 degrees Celsius.

An additional strategy we use is to keep our surgical scrub bins of chlorhexidine and alcohol warmed. We warm them in a warm water bath to about 39 degrees Celsius. This is also turned on first thing on the morning of surgery to ensure that the scrub is warm when needed.

Following the surgical procedure, the NHP is recovered in a recovery cage warmed by a warm-water circulating blanket and a Bair Hugger warm air blanket.

We hope that you find this information useful in your own battle!

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Academy of Surgical Research
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  - Orthopedic Research models
  - Advanced Anesthesia Topics and Animal Welfare
  - Veterinary Best Practices Effects on Rodent and Non-Rodent Studies
  - Implant Dentistry – Lessons from Animal Models
  - Microsurgical Models
  - Minimally Invasive Surgery
  - Medical Device Implantation
  - Novel Surgical Models
  - Surgical Research and IACUC/GLPs
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- **Wet Labs**
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    - Rabbit CV and Respiratory Telemetry Implantation
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