McGill

STANDARD OPERATING PROCEDURE #102

RABBIT ANALGESIA

1. PURPOSE

The intent of this Standard Operating Procedure (SOP) is to describe methods of assessing pain in rabbits and mitigating pain by administration of analgesic medications.

2. RESPONSIBILITY

Principal investigator (PI) and their research staff, veterinary care staff.

3. GENERAL CONSIDERATIONS

3.1. A procedure which would be expected to be painful if it were done on humans must be considered painful to the animal.

3.2. When there is a question of whether or not a procedure is painful, the animal should receive the benefit of analgesia.

3.3. Analgesia should be provided at an appropriate dose and frequency to control pain.

3.4. Any deviation from this procedure must be justified by the investigator and approved by the appropriate Facility Animal Care Committee (FACC).

4. PAIN RECOGNITION AND ASSESSMENT

4.1. Adapt the frequency of observation to the protocol (minimum once a day).

4.2. Start by observing the animal from a distance so the animal's behavior is not altered by the presence of the observer. Then proceed to observe the animal more closely.

4.3. Look for any changes in the behavior. Report animals which appear to be in pain to the veterinary care staff.

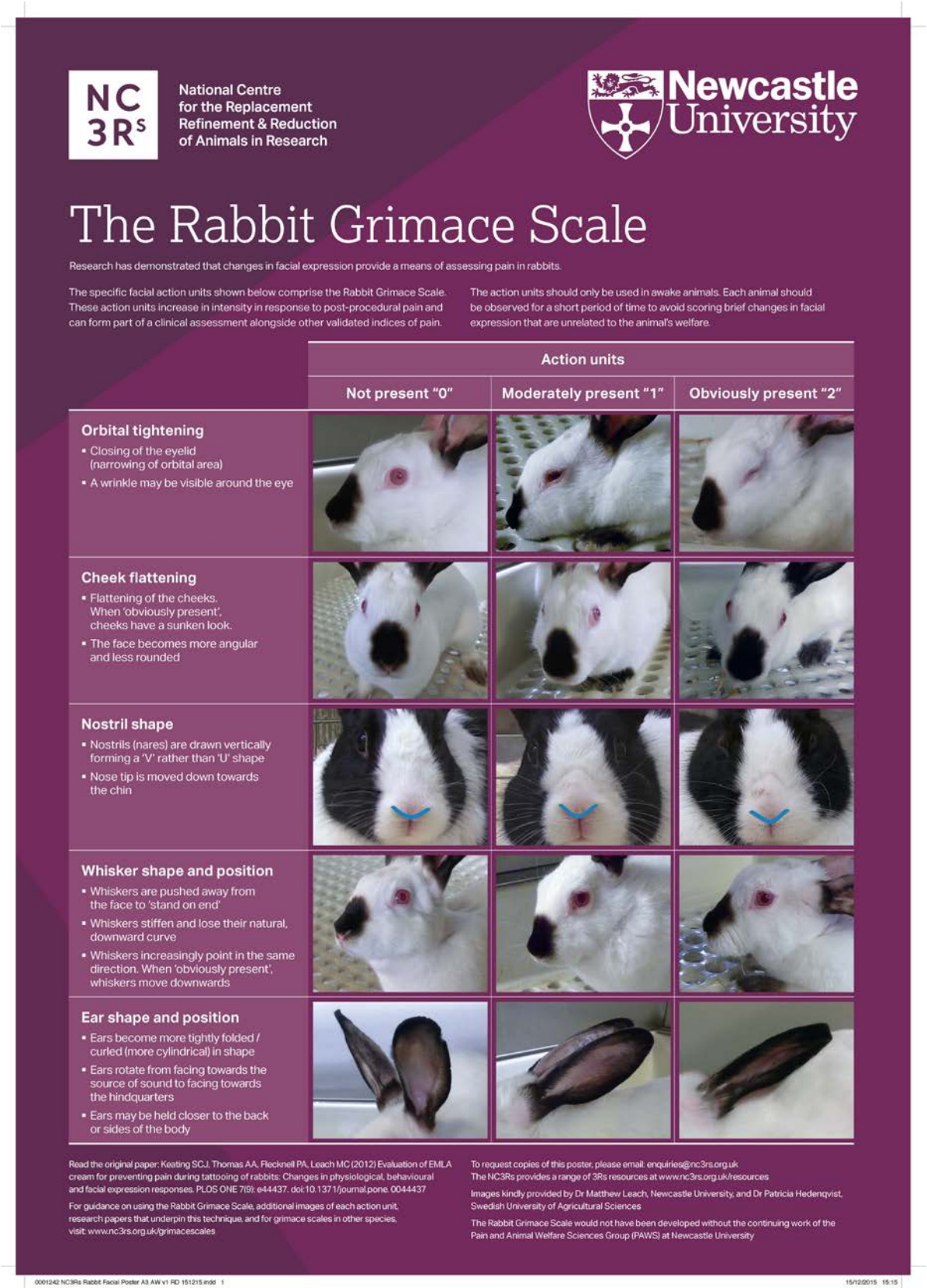
4.4. Common clinical signs indicative of pain or distress include:

- 4.4.1. Avoidance, vocalization and aggressiveness (mainly if the animal cannot escape)
- 4.4.2. Spontaneous activities are reduced. The animal is isolated from the social group
- 4.4.3. Altered gait
- 4.4.4. Hunched posture
- 4.4.5. Piloerection
- 4.4.6. Reduced grooming; dark-red stain around the eyes and at nostrils
- 4.4.7. Reduced appetite and subsequent weight loss

Note: The most reliable signs of pain and distress are the changes in behavior. This implies a good knowledge of species and individual normal behavior by the observer.

4.5. Rabbit Grimace Scale (Keating et al. 2012)

The rabbit grimace scale is a standardized behavioral coding system that demonstrates facial expressions which can be used to assess pain in the laboratory rabbit.



NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

Newcastle University

The Rabbit Grimace Scale

Research has demonstrated that changes in facial expression provide a means of assessing pain in rabbits.

The specific facial action units shown below comprise the Rabbit Grimace Scale. These action units increase in intensity in response to post-procedural pain and can form part of a clinical assessment alongside other validated indices of pain.

The action units should only be used in awake animals. Each animal should be observed for a short period of time to avoid scoring brief changes in facial expression that are unrelated to the animal's welfare.

	Action units		
	Not present "0"	Moderately present "1"	Obviously present "2"
Orbital tightening • Closing of the eyelid (narrowing of orbital area) • A wrinkle may be visible around the eye			
Cheek flattening • Flattening of the cheeks. When 'obviously present', cheeks have a sunken look. • The face becomes more angular and less rounded			
Nostril shape • Nostrils (nares) are drawn vertically forming a 'V' rather than 'U' shape • Nose tip is moved down towards the chin			
Whisker shape and position • Whiskers are pushed away from the face to 'stand on end' • Whiskers stiffen and lose their natural, downward curve • Whiskers increasingly point in the same direction. When 'obviously present', whiskers move downwards			
Ear shape and position • Ears become more tightly folded / curled (more cylindrical) in shape • Ears rotate from facing towards the source of sound to facing towards the hindquarters • Ears may be held closer to the back or sides of the body			

Read the original paper: Keating SCJ, Thomas AA, Flecknell PA, Leach MC (2012) Evaluation of EMLA cream for preventing pain during tattooing of rabbits: Changes in physiological, behavioural and facial expression responses. PLOS ONE 7(9): e44437. doi:10.1371/journal.pone. 0044437

For guidance on using the Rabbit Grimace Scale, additional images of each action unit, research papers that underpin this technique, and for grimace scales in other species, visit: www.nc3rs.org.uk/grimacescales

To request copies of this poster, please email: enquiries@nc3rs.org.uk
The NC3Rs provides a range of 3Rs resources at www.nc3rs.org.uk/resources

Images kindly provided by Dr Matthew Leach, Newcastle University, and Dr Patricia Hedenqvist, Swedish University of Agricultural Sciences

The Rabbit Grimace Scale would not have been developed without the continuing work of the Pain and Animal Welfare Sciences Group (PAWS) at Newcastle University

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5. ANALGESIA PLAN

5.1. If possible, provide analgesia before the painful stimulus, as it is more effective in preventing pain (e.g. give analgesic before surgery).

5.2. Try to use a combination of analgesics, which is often more effective than using a single agent.
For example, combination of buprenorphine, carprofen, and local infiltration of lidocaine/bupivacaine.

5.3. For surgical procedures, extend analgesia from pre-op to 72 hours post-op, unless otherwise specified in the Animal Use protocol (AUP) and approved by the FACC.

6. LOCAL ANALGESIA

6.1. Infiltrate or apply local analgesic to areas where a painful stimulus may be induced. Repeat application of local agent at specified intervals to maintain analgesia. In some cases a sedative is recommended when using local analgesia.

Analgesic	Dose	Duration	Note
Lidocaine	< 2 mg/kg	30–60 min.	Use lidocaine HCl 2% (20mg/ml) injectable solution. Because this drug is acidic, it is recommended to dilute it 3:1 with sodium bicarbonate injectable solution (at 5 or 8.4%). Dilution with sodium bicarbonate is not necessary if lidocaine is to be administered to an anesthetized animal. Dilution must be prepared immediately before use and should not be stored. Diluted solution is as effective but induction of analgesia is slightly prolonged.
Bupivacaine	< 2 mg/kg	3–4 hr.	Use bupivacaine HCl 0.50% (5mg/ml) injectable solution. Same comment as for lidocaine.
* Lidocaine-bupivacaine mixture	-	30min.-4 hr.	Same comment as for lidocaine. Combining both drugs allows for rapid induction and prolonged effect. Discard mixture after 3 months.
EMLA cream	Thick spread	30–60 min.	Shave or pluck the fur and apply a thick layer of cream ideally 10 minutes before the painful procedure.

*most commonly used

7. GENERAL ANALGESIA

Rabbit

Analgesic	Dose	Route	Frequency	Note
*Buprenorphine	0.05–0.1 mg/kg	Preferred: IM, IV, sublingual, gingival Other: SC	8–12 hr.	Mild to moderate pain. Controlled drug.
*Buprenorphine Slow Release (SR)	0.12 mg/kg	SC	Once	Buprenorphine SR (0.6mg/ml) is a sustained release buprenorphine product that has been developed to provide 72 hours of analgesia and is specifically designed for use in rodents. See administration instructions in section 7.2. Controlled drug.
*Carprofen	4-5 mg/kg	SC, PO	12–24 hr.	Mild to moderate pain.

Rabbit

Analgesic	Dose	Route	Frequency	Note
*Ketoprofen	2-5 mg/kg	SC, IM, IV	12–24 hr.	Mild to moderate pain.
*Meloxicam	0.3-0.5 mg/kg	SC, PO	24 hr.	Mild to moderate pain.
Fentanyl	25µg Patch		Every 3 days, starting 24h prior to surgery	Moderate to severe pain. Controlled drug.
Ketamine	0.1-1.0 mg/kg	SC, IM, IV	-	Moderate to severe pain. After initial bolus, constant rate infusion of 0.1-0.3 mg/kg/hr. Controlled drug.
Morphine-Lidocaine-Ketamine Combination	2 ml/kg/hr	IV	Constant rate infusion	Moderate to severe pain. To a 500ml bag of fluids, add morphine 60mg, lidocaine 750mg and ketamine 150mg. Controlled drugs.

*most commonly used

7.1. Administration of non-steroidal anti-inflammatory drugs (NSAIDs):

7.1.1. NSAIDs include carprofen, ketoprofen and meloxicam.

7.1.2. Ensure good water intake and monitor hydration status during the treatment period.

7.1.3. Suspend water restriction prior to administration of NSAIDs.

7.1.4. To minimize chances for adverse drug interactions, a washout period of 5-7 days is recommended before switching between NSAIDs.

7.2. Administration instructions for buprenorphine slow release (SR):

7.2.1. Avoid contact with the skin to prevent the development of injection site reactions.

7.2.2. Draw up the buprenorphine SR with an 18g needle and change to a 23g needle prior to administration

7.2.3. Administer subcutaneously on back of neck between the shoulder blades while the animal is anesthetized.

7.2.4. Administer slowly and finish injecting before the needle is pulled out through skin.

7.2.5. Pinch the injection site for approximately 10 seconds after removing the needle

7.2.6. Do not combine the buprenorphine SR with any other drugs in the same syringe and do not attempt to dilute the formulation.

8. REFERENCES

8.1. DiVincenti L Jr, Meirelles LA, Westcott RA. (2016). Safety and clinical effectiveness of a compounded sustained-release formulation of buprenorphine for postoperative analgesia in New Zealand White rabbits. *J Am Vet Med Assoc.* 2016 Apr 1;248(7):795-801.

8.2. Keating SCJ, Thomas AA, Flecknell PA, Leach MC (2012) Evaluation of EMLA Cream for Preventing Pain during Tattooing of Rabbits: Changes in Physiological, Behavioural and Facial Expression Responses. PLoS ONE7(9): e44437. https://doi.org/10.1371/journal.pone.0044437

SOP REVISION HISTORY

DATE	PREVIOUS VERSION	NEW VERSION
2015.04.22	6.1 (NO TEXT)	6.1 **Use lidocaine HCl 2% (20mg/ml) injectable solution.**
2015.04.22	6.1 (NO TEXT)	6.1 **Use bupivacaine HCl 0.50% (5mg/ml) injectable solution.**
2015.04.22	6.1 (NO TEXT)	6.1 Lidocaine-bupivacaine mixture: **Discard mixture after 3 months.**
2016.09.02	7. (NO TEXT)	7. Carprofen, ketoprofen and meloxicam: **Ensure good water intake and monitor hydration status.** **Suspend water restriction prior to administration.**
2016.09.06	7. Buprenorphine route of administration: SC	7. Buprenorphine route of administration: ~~SC~~ **Preferred: IM, IV, sublingual, gingival Other: SC**
2017.01.27	7.1 (NO TEXT)	**7.1. Administration of non-steroidal anti-inflammatory drugs (NSAIDs):** **7.1.1. NSAIDs include carprofen, ketoprofen and meloxicam.** **7.1.2. Ensure good water intake and monitor hydration status during the treatment period.** **7.1.3. Suspend water restriction prior to administration of NSAIDs.** **7.1.4. To minimize chances for adverse drug interactions, a washout period of 5-7 days is recommended before switching between NSAIDs.**
2017.02.13	4.5 Grimace Scale Image	4.5 Grimace Scale Image replaced with **NC3Rs poster image**
2017.10.17	7. (NO TEXT)	**Buprenorphine Slow Release (SR)** **Dose: 0.12 mg/kg** **Route of administration: SC** **Frequency: once** **Note: Buprenorphine SR (0.6mg/ml) is a sustained release buprenorphine product that has been developed to provide 72 hours of analgesia and is specifically designed for use in rodents. See administration instructions in section 7.2.** **Controlled drug.**
2018.10.12	7.2.6. Do not combine the buprenorphine SR with any other drugs and do not attempt to dilute the formulation.	7.2.6. Do not combine the buprenorphine SR with any other drugs **in the same syringe** and do not attempt to dilute the formulation.