Thermal and mechanical nociceptive threshold testing in pregnant sheep

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Background

Despite the extensive use of sheep in biomedical research, there is limited information on the efficacy of peri-operative analgesic drugs for this species. Furthermore, pregnancy may preclude the use of non-steroidal anti-inflammatory drugs.

Hypothesis

Post-operative analgesia is not inferior in pregnant ewes receiving intra-peritoneal medetomidine (3 µg/kg/h) compared to a transdermal fentanyl patch (75 µg/h) placed at the end of surgery.

Aims

We aimed to compare two analgesic regimes in pregnant ewes following a laparotomy by measuring thermal and mechanical nociceptive thresholds (TT and MT respectively).

Materials and Methods

Approval was granted by the Animal Ethics Committees of Murdoch University and the University of Western Australia. Pregnant ewes at 128 days of gestation were anaesthetised and underwent a ventral midline laparotomy and hysterotomy as part of another research project. The anaesthetic protocol was standardised:

- Pre-anaesthetic medication
  - acepromazine (0.03 mg/kg) and
  - buprenorphine (0.01 mg/kg) by intramuscular injection
- Induction of anaesthesia 30 minutes later
  - diazepam (0.25 mg/kg) and
  - ketamine (5 mg/kg) by intravenous injection
- Maintenance of anaesthesia
  - isoflurane in 100% oxygen
  - volume cycled ventilation to maintain normocapnia
  - intravenous Hartmann's solution to manage hypotension

At the end of surgery (~60-90 minutes) the ewes were divided into 2 groups:

Intraperitoneal medetomidine (IPM)

- an osmotic pump loaded to deliver 3 µg/kg/h of medetomidine was placed in the peritoneal cavity immediately prior to closure of the abdomen (Figure 1)

Fentanyl patch (FP)

- a 75 µg/h fentanyl patch was placed on the medial aspect of the thigh (equivalent to 1.1-1.4 µg/kg/h) (Figure 2)

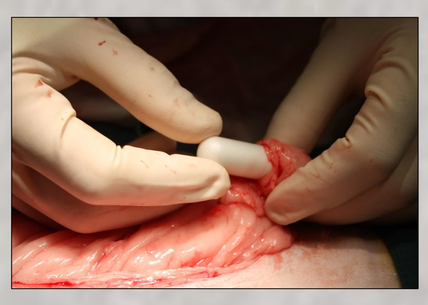

Figure 1: *A 2 mL Alzet® osmotic pump (10 µL/h) secured in a pocket of omentum for intra-peritoneal delivery of medetomidine. Pumps were primed for 12 hours prior to placement in the abdominal cavity.*

Figure 2: *A Fentanyl patch on the medial thigh.*

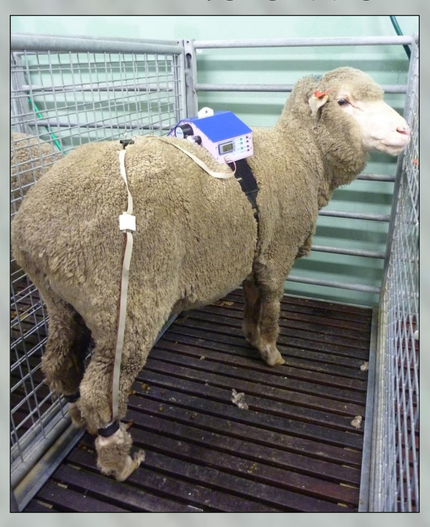

Figure 3: *Thermal and mechanical stimuli were delivered to opposing hindlimbs.*

Figure 4: *Thermal and mechanical stimuli were delivered to opposing hindlimbs.*

TT and MT (Topcat Metrology Ltd) were measured by 2 observers (GM and FM): pre-operative baseline and post-operatively at 2, 6, 24 and 48 h.

At each time point each test was performed 5 times, alternating thermal and mechanical stimuli, with 10 minutes between thermal stimuli to allow for cooling of the probe and the skin.

Thermal stimuli site: lateral aspect of the metatarsus via a probe mounted onto clipped skin (cut out 60 °C).

Mechanical stimuli site: the contralateral limb via a pneumatically driven 1.5 mm diameter pin (Figures 3 and 4).

Data were analysed using the Kruskal-Wallis rank sum test ($p<0.05$). Once a significant effect was identified, pairwise comparisons were performed using paired Wilcoxon rank sum tests. To compensate for multiple hypotheses testing, $p<0.005$ was considered significant.

Results

	Initial skin temperature °C (SD)	Thermal threshold (TT) °C (SD)	Mechanical threshold (MT) Newtons (SD)
Intraperitoneal medetomidine (IPM, n=8)			
Pre-op	34.7 (0.7)	55.6 (5.5)	8.0 (5.0)
Post-op 2 h	34.0 (1.0)	59.2 (3.0)*	6.2 (3.0)
Post-op 6 h	34.0 (0.8)	58.4 (4.1)	6.9 (4.6)
Post-op 24 h	33.1 (0.8)	56.7 (5.4)	8.3 (5.8)
Post-op 48 h	33.3 (1.3)	55.2 (6.4)	8.0 (5.3)
Fentanyl patch (FP, n=8)			
Pre-op	34.2 (1.0)	56.1 (5.0)	5.3 (2.6)
Post-op 2 h	34.5 (0.5)	57.6 (5.0)	8.2 (4.8)
Post-op 6 h	34.2 (0.7)	57.0 (3.7)	7.0 (4.3)
Post-op 24 h	33.4 (0.9)	55.2 (5.1)	8.1 (5.0)
Post-op 48 h	33.4 (1.6)	54.2 (5.6)	7.1 (4.5)

* $p = 0.003$ Post-op 2 h compared to pre-op

There were no statistically significant differences in initial skin temperature between IPM and FP, nor over time. The increase in the TT 2 hours post-operatively was statistically significant in the sheep receiving IPM ($p = 0.003$), but not in the sheep in the FP group. The changes in MT were not statistically significant between or within groups.

Recovery from anaesthesia was comparable between the 2 groups and sedation was not observed in either group.

Discussion

A decrease in either TT or MT from the pre-operative measurement is indicative of hyperalgesia. Conversely, an increase in these values from the pre-operative measurement suggests that analgesic therapies are effective. This study suggests that sheep treated with IPM are provided with analgesia in the immediate post-operative period. We were unable to demonstrate a prolonged effect of IPM or any analgesic effect of FP within the 48 hour study.

There are a number of limitations to this study: there is no negative control; the analgesic effects of drugs included in the anaesthetic regime may confound the results; and the site of testing was distal to the surgery site. An analgesia free control group was not possible, given ethical considerations, and the anaesthetic regime was standardised. Applying thermal and mechanical stimuli to the ventral abdomen of the sheep was unrewarding so the hindlimb site was selected after pilot tests of a number of sites.

Conclusions

Intra-peritoneal medetomidine (3 µg/kg/h) appears to have a role in post-operative analgesia for pregnant sheep. Hyperalgesia was not observed with either protocol.