

1A-119 USING AN ANTI-INFLAMMATORY TO INCREASE PIGLET SURVIVAL AND GROWTH RATES

Report prepared for the
Co-operative Research Centre for High Integrity Australian Pork

By

Kate Plush, John Pluske, David Lines, Cameron Ralph and Roy Kirkwood

SunPork Solutions, Murdoch University, SunPork Farms, Agersens and The University of
Adelaide

October 2018



Australian Government
Department of Industry,
Innovation and Science

Business
Cooperative Research
Centres Programme

Executive Summary

It is assumed that parturition is painful for sows, and the level of pain experienced may be heightened under farrowing crate housing. Sow discomfort following parturition has been linked to increased piglet mortality. Parturition is also associated with a sub-acute inflammatory response that in dairy cows, has been shown to reduce milk output. The limited amount of work that has been conducted on anti-inflammatory administration in sows has shown that there are benefits, with improvements in sow body condition and piglet colostrum intake and growth reported. To date, the impact of anti-inflammatory administration prior to farrowing has not been tested. In this experiment, we hypothesised that a non-steroidal (NSAID) and steroidal (SAID) injection given to the sow prior to farrowing would improve sow wellbeing, increase feed intake, and subsequently improve piglet survival and growth.

One hundred and forty-nine sows were randomly allocated to one of three treatments; NSAID sows injected with meloxicam, SAID sows injected with dexamethasone, and CONTROL sows injected with saline on d114 (and again on d116 if they had not farrowed). Following farrowing, the level of injuries on the sows face was assessed and the number of piglets born alive and born dead was noted. On d2, a blood sample was collected from the sow for markers of distress and inflammation, and from the piglet for brix refractometer analysis as an indicator of colostrum intake. The rectal temperature of the sow was recorded daily for the first three days. Sow feed intake was measured daily, and litters were weighed on d1 and again on d21 of lactation.

NSAID treated older parity sows (P5+) gave birth to fewer liveborn and more stillborn piglets when compared with the SAID and CONTROL groups. Facial injuries were reduced in parity two to four sows by SAID administration. There was no treatment effect on rectal temperature of the sows, or incidence of mastitis, but piglet serum protein levels tended to be reduced in the NSAID litters. None of the plasma markers of inflammation and stress were altered by treatment. Whilst average feed intake was improved by both NSAID and SAID medication, piglet mortality and growth remained unaffected. Farrowing rate after subsequent re-breeding was reduced by almost 40% in the NSAID treatment.

In conclusion, NSAID's should not be administered prior to farrowing for older parities as there is an increased risk of intra-partum piglet death, as well as poorer immunoglobulin uptake in the piglets. NSAID treatment also significantly reduced subsequent re-breeding success. There was some indication that SAIDs improved sow-wellbeing leading up to farrowing, and improved sow feed intake, but pre-partum anti-inflammatory injection does little to improve postnatal piglet survival or growth.

Table of Contents

Executive Summary.....	i
1. Introduction.....	1
2. Methodology	2
3. Outcomes	4
4. Application of Research.....	10
5. Conclusion.....	11
6. Limitations/Risks	11
7. Recommendations	12
8. References	12
Appendices	Error! Bookmark not defined.
<i>Appendix 1:</i>	<i>Error! Bookmark not defined.</i>

1. Introduction

Animals are equipped with sensory mechanisms that detect pain and, in most cases, this results in an appropriate response that maintains homeostasis and prevents injury (Almeida *et al.* 2004). There are however life history stages where pain is necessary and unavoidable; parturition is one of these times. The environment in which sows are housed for parturition has been suggested to be uncomfortable, and so may result in soreness and injury prior to farrowing (Hausmann *et al.* 1999). Additionally, confinement within a farrowing crate prohibits nest-building behaviour leading up to farrowing, reducing circulating oxytocin levels (Viitasaari *et al.* 2014). In rats, there is evidence that central oxytocin has analgesic properties (Pettersson *et al.* 1996). Therefore, housing in farrowing crates may result in amplified pain for sows, and behavioural indicators would support this notion (Nowland *et al.* 2017). Parturition pain is also associated with the release of opioids (Jarvis *et al.* 1997) that inhibit oxytocin release (Douglas and Russell 2001). Treatment with an opioid antagonist shortens parturition while increased pain during parturition increases sow movements, which could prove dangerous to newborn piglets (Jarvis *et al.* 1999). If it is accepted that providing sows with pain relief to decrease opioid secretion could accelerate the farrowing process, the provision of an anti-inflammatory may also improve post-natal piglet survival.

Lactation requires a shift in nutrient utilization that depends on adaptations in the liver, gut, adipose tissue, muscle and bone, in addition to the mammary gland. Lactation typically increases energy and nutrient requirements, which are usually met by an elevation of food intake and a mobilisation of body's energy stores. In dairy cows, lactation has been shown to induce immune and inflammatory responses in the liver (Lor *et al.* 2005), and the presence of an acute phase protein (APP) response in post-partum dairy cows is well-established. Although early studies focused on associations between inflammatory markers and diseases such as mastitis and metritis, numerous studies in the past decade have demonstrated that inflammatory and APP mediators are elevated in the days after parturition, even in cows that are apparently healthy (Mullins *et al.* 2012). Unlike inflammation associated with a local infection, the post-partum inflammatory state has no clear focal organ and does not necessarily induce the traditional signs of inflammation (fever, swelling, pain). Rather, inflammation during this period is systemic and sub-acute, consistent with the concept of metabolic inflammation. Studies have clearly demonstrated that treatments that reduce the inflammatory response in the immediate post-partum period, such as anti-inflammatory medications, can increase milk yield (Farney *et al.* 2013). In contrast to extensive research in cows on mechanisms underlying the lactation-induced metabolic and immunologic adaptations, only limited information is available in sows.

Viitasaari *et al.* (2013) reported that sows treated with the non-steroidal anti-inflammatory drug (NSAID) ketoprofen maintained back fat better during lactation when compared with the control group, and consequently the severity of shoulder sores was reduced after farrowing. Piglet growth was unaffected in this study, as well as in Mainau *et al.* (2012) who administered meloxicam, a NSAID, to the sow.

However, these studies did not contain a large enough sample size to detect changes in piglet growth as a measure of milk yield. Tenbergen *et al.* (2014), with a larger sample size, also reported no improvement in piglet average daily gain when meloxicam was administered to sows 12 h after birth, but the delay in treatment administration following parturition may explain these unexpected findings. Mainau *et al.* (2016) demonstrated that an oral dose of meloxicam to the sow at the birth of the first piglet improved colostrum intake, piglet average daily gain and weaning weight. The impacts of glucocorticoids (e.g., dexamethasone) remain to be elucidated and they are likely to be a better candidate for reducing pain and inflammation during parturition and in the peri-natal period due to their ability to act at multiple sites/levels. Therefore, administration of an anti-inflammatory compound before farrowing might improve piglet survival and growth.

2. Methodology

Animals

This experiment was conducted at a South Australian 7,500 sow breeder unit during summer months in 2018. One hundred and forty-nine multiparous sows (3.8 ± 0.1) entered farrowing accommodation 4.9 ± 0.2 days prior to farrowing. No sows were induced to farrow, and the farrowing process occurred over an 8-day period with an average gestation length of 116.6 ± 0.2 days. Sows were fed 2.5 kg/d of lactation sow mash formulated to provide 14.25 DE MJ/kg from entry to the farrowing shed until the day of farrowing and, thereafter, fed *ad libitum* until weaning (hoppers held ~ 7.5kg of feed and feed was delivered twice daily). The date of farrowing was recorded once daily between 0700 and 1000, and piglet fostering occurred after this event. Fostering was minimal and piglet movement only occurred when the number of piglets exceeded the number of functional teats available. In this event, spilt suckling was carried out prior to piglet relocation according to the procedures of Huser *et al.* (2015), in order to ensure more equal colostrum intake across the litter. After the initial fostering event, which occurred within treatment where possible, piglets were only removed from the sow if they were losing condition and at this point they were removed from the experiment and recorded as 'ill thrift'. The litters were weaned at 25.4 ± 0.1 days.

Housing

Sows were housed in conventional farrowing crates within 1.8 m x 2.4 m pens having fully slatted plastic flooring and provided the sow with a feed hopper, two nipple drinker lines (one for standing and one for lying access), and a triangular creep area with solid flooring and heat lamp for the piglets. The farrowing shed contained 237 identical crates placed in three rows and was naturally ventilated. Due to this natural ventilation of the shed, the lighting regime followed daylight hours (0600 to 2000).

Treatments

At d 114 of gestation, sows were randomly allocated to one of three treatments. Control sows received 10 ml saline, SAID sows 1 ml/20 kg dexamethasone (2

mg/ml Dexason, Troy Laboratories AUST), and NSAID sows 1 ml/50 kg meloxicam (2 mg/ml Recocam, Bimeda AUST). All sows received treatment via intramuscular injection using 18 g needles and 20 ml syringes. Sows were injected at 1500 h on day 114 and again on day 116 if they had failed to farrow. After treatment all sows were managed similarly.

Measurements

On the day of farrowing, sow location, parity and litter details (total born, born alive, and born dead) were noted and sows were inspected for facial injuries. The following score was applied to each sow based on the escalation of injuries from the nose to the ear as an indication of stereotypic behaviour directed towards crate features:

- Score 0: sow presents with no fresh injuries.
- Score 1: some fresh abrasions mainly concentrated on the tip of nose of the sow.
- Score 2: fresh abrasions are easily detected on the nose of the sow, and there may be abrasions present on other areas further up the nose and close to the eye.
- Score 3: Numerous abrasions are evident on the nose area, as well as around the eyes, head and ears of the sow.

Rectal temperatures of each sow were recorded at 1400 h on days 1, 2 and 3 after farrowing, and evidence of mastitis or metritis (temperature greater than 40°C) was recorded. If a sow presented with mastitis or metritis they were medicated with penicillin as per veterinary instruction but did not receive any further anti-inflammatory medication.

A 10 ml blood sample was collected on day 2 of lactation from 20 sows per treatment via jugular venepuncture using an 18 g needle and heparinised vacutainer, after restraint by snare. This sample was stored on ice until centrifugation and plasma stored frozen in duplicate at -20°C. At this same time, three piglets were selected at random from this subset of sows, and blood was collected via jugular venepuncture using a 23 g needle, 5 ml syringe and serum tube. The sample was refrigerated overnight and then assessed for protein percentage using Brix refractometry for an indication of colostrum intake (Manjarín *et al.* 2018).

The number of piglets present in the litters and the litter weights were recorded after fostering at day one and again at day 21. The average piglet weight on these two measurement days was calculated by dividing the litter weight by the number of piglets. All piglet mortalities and causes were recorded.

Sow feed intake was measured using a feed cart which had been converted to scales by placing two load cells under the feed bin wired to an indicator located on the handle of the cart. This scale was calibrated daily by adding 10 kg weights until the load reached 100 kg. Due to almost no feed wastage being observed, the feed delivered to sows at 1600 h and 0700 h the following day was assumed to be feed intake. This was recorded until day 21.

Laboratory analysis

Sow plasma samples were analysed for cortisol, 13,14-dihydro-15-keto-prostaglandin F2-alpha metabolite (PGFM), and haptoglobin concentrations as markers of stress and inflammation. Cortisol concentration was determined by radioimmunoassay (#07221102, MP Biomedicals, NSW Australia) with average intra and inter assay coefficients of variation (CV) of 25% and 6.7%, respectively. The PGFM analyses was conducted using an ELISA (#MBS7214882, Resolving Images, VIC Australia) with average intra and inter assay CV of 12% and 20%, respectively. Haptoglobin analyses were conducted using an ELISA (#ab205091, Abcam, VIC Australia) with intra and inter assay CVs of 2.6% and 6.0%, respectively.

Statistics

All data were analysed in SPSS Statistics V24 (IBM, USA). Unless otherwise specified, a general linear model was applied with the fixed effects of room (1 to 4), parity group (2 to 4, or 5+), treatment (CON, SAID or NSAID), and the interaction between parity and treatment. The facial injury score and all piglet deaths (born dead, pre-foster mortality, post foster mortality, liveborn mortality, and total mortality) were analysed using a generalised linear model with Poisson distribution and the same model. The number of piglets born dead also contained the covariate of total born. Sow feed intake was analysed using a repeated measures linear mixed model with sow as the subject and day as the repeated measure. Room, parity group, treatment, day (1 to 21) and the interactions parity group by day, treatment by day, and parity group by treatment by day were included in the model as fixed effects.

3. Outcomes

The average gestation length was 116.5 ± 0.3 days and was unaffected by treatment. The farrowing performance of the sows is outlined in Table 1. There was no overall treatment effect on the total number of piglet born within a litter, or the number of piglets born dead, but there was a tendency for the number of piglets born alive to be reduced in the NSAID treatment ($P = 0.103$). The treatment by parity interaction was significant for both piglets born alive and stillbirths. NSAID treated sows in the parity 5+ group gave birth to fewer liveborn and more stillborn piglets (Figure 1; $P < 0.05$).

Table 1. Farrowing performance (mean \pm SEM number of piglets per litter) of sows injected with saline (Control), a non-steroidal anti-inflammatory (NSAID) or steroidal anti-inflammatory (SAID) prior to the farrowing event.

	Control		NSAID		SAID		<i>P-value</i>
	Mean	SEM	Mean	SEM	Mean	SEM	
Total born	13.9	0.7	12.5	10.6	13.8	0.6	0.162
Born alive	12.9	0.6	11.4	0.5	12.7	0.5	0.103
Born dead	0.56	0.13	0.9	0.14	0.81	0.13	0.179

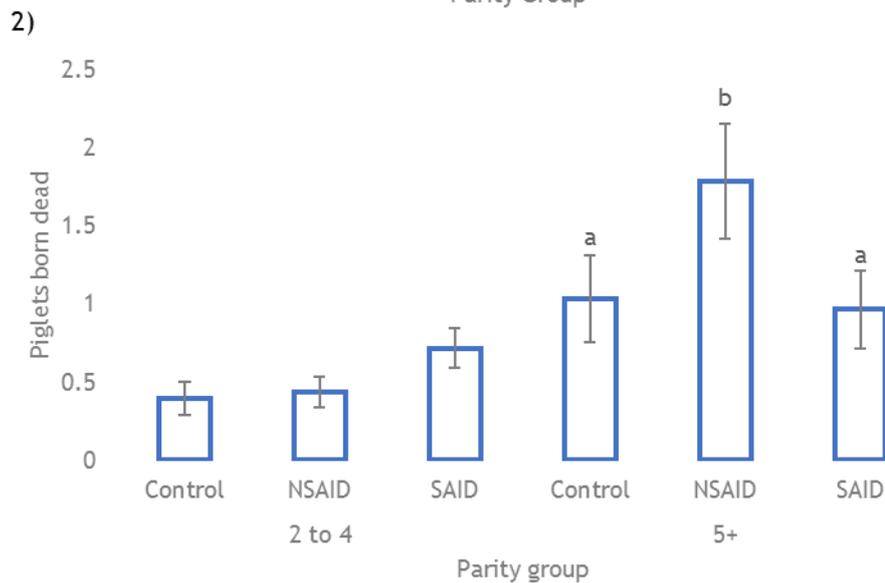
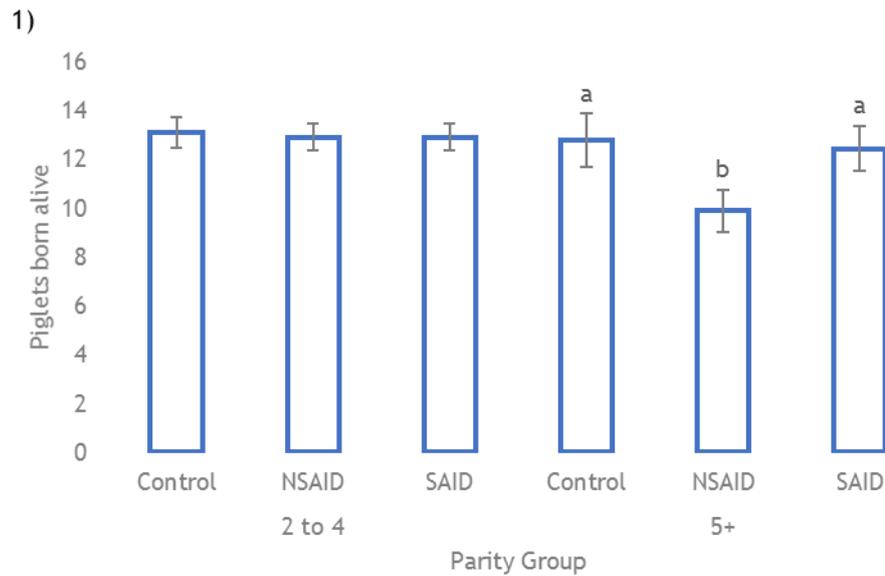


Figure 1. The mean \pm SEM number of piglets born alive (1) and dead (2) per litter for sows of parity 2 to 4 or 5+ injected with either saline (Control), a non-steroidal anti-inflammatory (NSAID), or steroidal anti-inflammatory (SAID) prior to farrowing. ^{a,b} represents a significant difference ($P < 0.05$) within parity group.

There was no main effect of treatment for facial injury score ($P > 0.05$). However, within parities 2 to 4, SAID sows presented with a lower score than Control, with NSAID sows intermediate (Figure 2; $P < 0.05$)

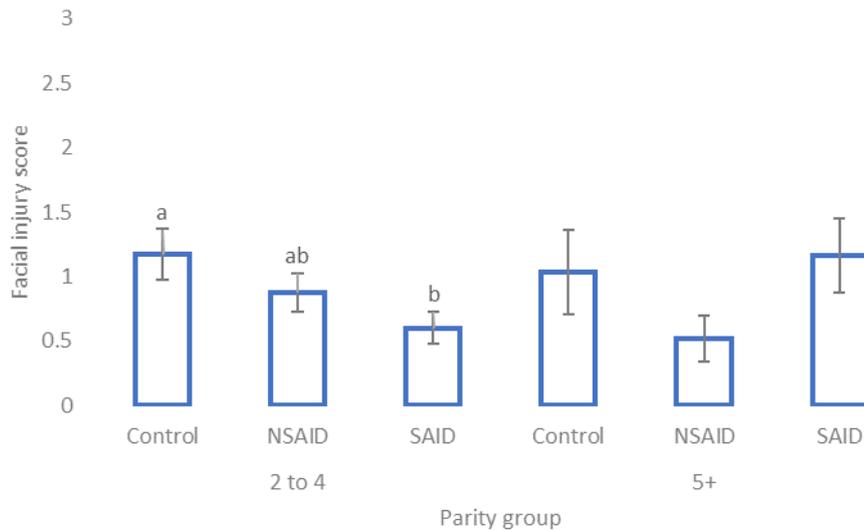


Figure 2. The mean \pm SEM facial injury score (with 0 being no injury, and 3 being high level of injury) for sows of parity 2 to 4 or 5+ injected with either saline (Control), a non-steroidal anti-inflammatory (NSAID), or steroidal anti-inflammatory (SAID) prior to farrowing. ^{a,b} represents a significant difference ($P < 0.05$) within parity group.

There was no treatment effect on the rectal temperatures of sows over the first 3 days of farrowing, nor the incidence of mastitis over this period (Table 2). There was a tendency for piglets born to sows from both the NSAID and SAID treatments to record lower serum protein concentrations at 24 h of age when compared to those born from Control sows ($P = 0.102$).

Table 2. Mean \pm SEM sow rectal temperature recorded daily for three days post farrowing, the incidence (%) of mastitis ($>40^{\circ}\text{C}$) over the 3-d recording period, and piglet serum protein (%) at 24h of age for sows injected with saline (Control), a nonsteroidal anti-inflammatory (NSAID) and steroidal anti-inflammatory (SAID) prior to the farrowing event. † 95% Confident Intervals presented rather than SEM for binary data.

		Control		NSAID		SAID		<i>P</i> -value
		Mea	SEM	Mea	SEM	Mea	SEM	
Rectal temperature ($^{\circ}\text{C}$)								
	Day 1	38.9	0.1	38.8	0.1	39.0	0.1	0.349
	Day 2	38.9	0.1	38.9	0.1	38.7	0.1	0.254
	Day 3	38.8	0.1	38.7	0.1	38.8	0.1	0.444
			(9-		(2-		(6-	
	Incidence of mastitis (%)†	19	35)	7	17)	12	25)	0.211
	Piglet serum protein (%)	6.5	0.4	5.5	0.4	5.7	0.4	0.102

Treatment had little impact on sow plasma cortisol or PGFM concentrations on day 2 (Table 3; $P > 0.05$). Parity tended ($P = 0.1$) to influence cortisol concentration, with parity 5+ sows displaying increased concentrations compared to those of

parity 2 to 4. PGFM was reduced in 5+ sows compared to younger sows ($P < 0.05$). Treatment had little impact on haptoglobin concentration, but there was a trend for reduced levels in older sows ($P = 0.058$).

Table 3. Day 2 plasma sqrt cortisol, PGFM and haptoglobin concentrations in sows injected with either saline (Control), a nonsteroidal anti-inflammatory (NSAID), or steroidal anti-inflammatory (SAID) prior to farrowing, and those of parity 2 to 4 and 5+. † Back-transformed means are presented in brackets.

	Treatment						<i>P</i> -value	Parity				<i>P</i> -value
	Control		NSAID		SAID			2 to 4		5+		
	Mean	SEM	Mean	SEM	Mean	SEM		Mean	SEM	Mean	SEM	
Sqrt cortisol (nmol/ml)†	7.9	0.8	8.7	1	6.3	0.9	0.176	6.8	0.6	8.5	0.9	0.100
	(62.4)		(75.7)		(39.7)			(46.2)		(72.3)		
PGFM (ng/ml)	4.7	0.6	3.2	0.7	4	0.6	0.271	4.8	0.4	3.1	0.6	0.023
Haptoglobin (mg/ml)	1.4	0.1	1.4	0.2	1.2	0.1	0.387	1.5	0.1	1.2	0.1	0.058

There was no impact of treatment on the total number of piglet deaths or deaths from sow overlay of low piglet viability on days 1 or 2 (Table 4; $P > 0.05$). Similarly, piglet mortality across all stages or piglet removal failed to be influenced by treatment (Figure 3; $P > 0.05$). Whilst most stages of mortality remained unaffected by parity, total deaths (the sum of piglets born dead and postnatal mortality) was increased in parity 5+ sows (2.8 ± 0.3 piglets) when compared with parity 2 to 4 sows (2.1 ± 0.1 piglets; $P < 0.05$).

Table 4. Mean \pm SEM total number, overlay, or low viability piglet deaths per litter on days 1 and 2 for those born to sows injected with saline (Control), a nonsteroidal anti-inflammatory (NSAID) and steroidal anti-inflammatory (SAID) prior to the farrowing event.

		Control		NSAID		SAID		<i>P</i> -value
		Mean	SEM	Mean	SEM	Mean	SEM	
Day 1	Total	0.54	0.13	0.54	0.11	0.44	0.11	0.770
	Overlay	0.42	0.11	0.43	0.1	0.3	0.08	0.544
	Low viable	0.08	0.05	0.07	0.04	0.12	0.06	0.797
Day 2	Total	0.18	0.09	0.25	0.08	0.25	0.07	0.825
	Overlay	0.15	0.08	0.12	0.07	0.18	0.06	0.837
	Low viable	0.03	0.03	0.07	0.04	0.08	0.04	0.591

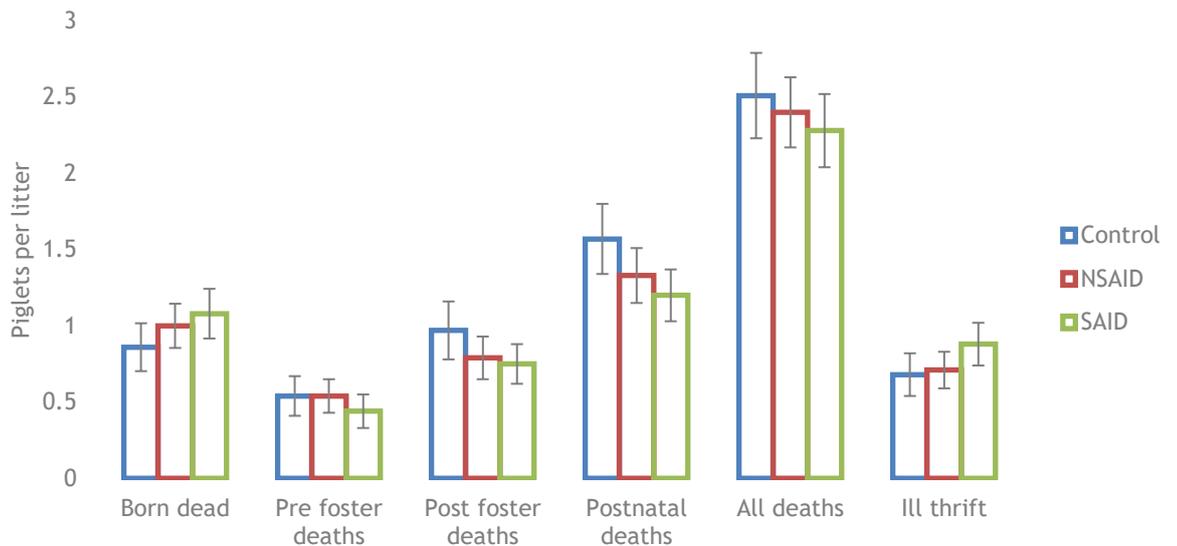


Figure 3. Mean \pm SEM piglet deaths recorded at birth, prior to fostering, after fostering, postnatal deaths (the sum of pre and post foster deaths), all piglet deaths (the sum of piglets born dead and postnatal deaths), and piglet removal for ill thrift from sows injected with either saline (Control), a nonsteroidal anti-inflammatory (NSAID), or a steroidal anti-inflammatory (SAID) prior to farrowing.

The number and weight of piglets at day 1 and day 21 of age were unaffected by treatment (Table 5; $P > 0.05$). Parity did not influence any of the measures at day 1, but litter size at day 21 was reduced in the 5+ group compared with the 2 to 4 sows (9.2 ± 0.3 versus 9.8 ± 0.2 pigs respectively; $P < 0.05$). A similar pattern was observed for day 21 litter weight (5+: 57.5 ± 2.0 kg, and 2 to 4: 63.3 ± 1.2 kg; $P = 0.01$), but average piglet weight was unaffected ($P > 0.05$). Feed intake was affected by day (Fig. 4; $P < 0.001$) and treatment (Table 5; $P = 0.001$), but the interaction between day and treatment was not significant (Figure 4; $P > 0.05$). There was no effect of sow feed intake on piglet growth. Sows of parity 2 to 4 displayed a higher average daily feed intake (7.6 ± 0.1 kg) than those of parity 5+ (7.0 ± 0.1 kg; $P < 0.001$).

Table 5. Mean \pm SEM litter size, litter and average piglet weight measured on day 1 and day 21, as well as the average lactation feed intake for sows injected with saline (Control), a nonsteroidal anti-inflammatory (NSAID) and steroidal anti-inflammatory (SAID) prior to the farrowing event.

	Control		NSAID		SAID		<i>P</i> -value
	Mea n	SE M	Mea n	SE M	Mea n	SE M	
Litter size fostered to	11.2	0.2	11.3	0.1	11.2	0.2	0.897
Litter weight day 1 (kg)	14.8	0.6	15.3	0.5	15.1	0.5	0.838
Average piglet weight day 1 (kg)	1.3	0	1.4	0	1.4	0	0.825
Litter size day 21	9.5	0.3	9.6	0.2	9.4	0.3	0.887
Litter weight day 21 (kg)	60.3	2.1	61.2	1.8	59.7	1.9	0.841
Average piglet weight day 21 (kg)	6.3	0.1	6.4	0.1	6.4	0.1	0.714

Average sow feed intake per day (kg)

7.0^a 0.1 7.4^b 0.1 7.5^b 0.1 0.001

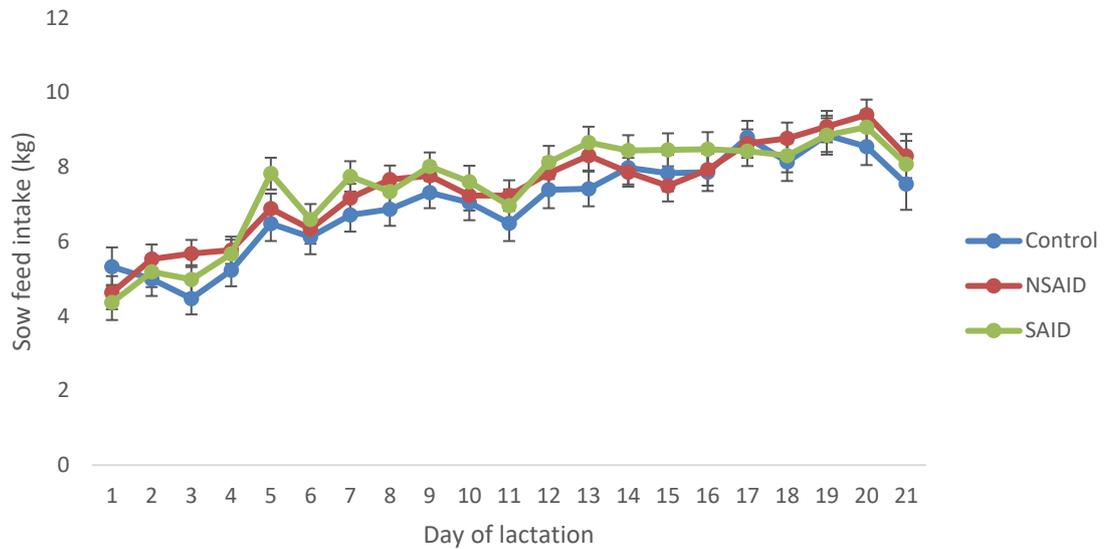


Figure 4. Mean \pm SEM daily feed intake of sows injected with saline (Control), a nonsteroidal anti-inflammatory (NSAID) and a steroidal anti-inflammatory (SAID) prior to the farrowing event.

After weaning, there was a tendency for treated sows to return to oestrus sooner, with more SAID sows bred within 7 days. However, compared to controls, farrowing rates were lower ($P < 0.05$) for NSAID sows with SAID sows being intermediate (Table 6).

Table 6. Effects on subsequent reproductive performance for sows injected with saline (Control), a nonsteroidal anti-inflammatory (NSAID) or steroidal anti-inflammatory (SAID) prior to the previous farrowing event; means \pm SEM. ^{a,b} represents a significant difference ($P < 0.05$) within measure.

	Control		NSAID		SAID		<i>P</i> -value
	Mea	SEM	Mea	SEM	Mea	SEM	
Wean to service interval (days)	9.2	1.5	7.3	1.1	4.4	2.2	0.098
Bred within 7 days (%)†	71	86	70	87	85	95	0.199
Farrowing rate (%)	89 ^a	96	58 ^b	80	70 ^{ab}	87	0.045
Litter size (pigs)	14.9	0.9	15.8	1	14.5	1	0.32

†, Means with 95% confidence intervals

4. Application of Research

To the authors' knowledge, this is the first study examining the influence of administering anti-inflammatory products prior to farrowing on sow wellbeing and piglet survival and growth. Products were chosen to be administered before farrowing as previous work where NSAIDs were given 12-24 h after farrowing failed to elicit any benefits. Facial injury scores were used as an indirect measure of sow discomfort with more stereotypes targeted towards crate fixtures, and hence face damage. Lower scores in the SAID-treated sows suggests the dexamethasone treatment improved sow wellbeing. This treatment also improved sow lactation feed intake, but this failed to translate to any improvements in piglet survival and growth.

Treatment with a SAID or NSAID increased sow feed intake, which may indirectly indicate an improved sow well-being. In support, the feed intake effect was most pronounced during days 2-5 after farrowing, possibly indicating an improved post-partum recovery. The feed intake data support earlier work where sows lost less body condition and presented with fewer shoulder sores after ketoprofen administration (Viitasaari *et al.* 2013). However, no relationship between sow feed intakes and pre-weaning piglet growth and survival were detected in the current study. This suggests that within the feed intakes observed, milk yield was not a compensable effect; ie. milk yields will decrease with very low feed intakes but, beyond a certain point, will not increase with increasing feed intake.

Older parity sows treated with the NSAID gave birth to more stillborn and, consequently, fewer liveborn piglets. Anti-inflammatory drugs act by inhibiting prostaglandin synthesis (Simmons *et al.* 2004), hence the finding that stillbirths were increased in older parity sows from this treatment is not surprising. Prostaglandins are pivotal for the contraction of smooth muscle and hence for the uterus to expel the foetus during birth. If prostaglandin concentrations were reduced in this tissue by the NSAID treatment, this could have delayed the birth of piglets and resulted in the observed increase in intra-partum death. That this was most evident in the older sows may indicate a clinically unapparent hypocalcaemia due to repeated lactations accentuating the anti-prostaglandin effect on uterine contractions.

That a similar effect was not evident for SAID-treated sows implies multiple modes of action. In human medicine, NSAIDs are not given to women in late gestation because of possible effects on the unborn child. This includes an adverse effect on the ductus arteriosus whose patency is maintained by prostaglandins. It has been demonstrated that NSAIDs can cross the placental barrier and enter the foetal circulation (Antonucci *et al.* 2012). An associated depressed prostaglandin level could impact cardiovascular health in addition to adverse effects on brain, kidney, lung, and gastrointestinal tract (Antonucci *et al.* 2012). It is reasonable to assume the same is true for pigs with the possible consequence of more stillbirths. Corticosteroids also depress prostaglandins but an effect of the SAID treatment on stillbirths was not apparent in the present study. This may involve the known increase in pre-partum corticosteroid binding globulin (CBG) (Challis *et al.* 1995).

The administered dexamethasone is more potent than endogenous corticoids, but fetal blood levels would be expected to be very low and bound to CGB, so limiting effects on prostaglandin synthesis.

Interestingly, piglet serum protein levels, as a measure of colostrum transfer, tended to be lower in the NSAID piglets, which contrasts with previous results (Mainau *et al.* 2016). However, this investigation administered the NSAID during parturition while in the current study it was administered pre-partum. Given that the increase in stillbirths in the NSAID treatment is likely indicative of farrowing difficulties, then and inadvertently, hypoxia might have increased thereby reducing piglet vigour, which in turn would reduce colostrum intake. No treatment differences in sow cortisol levels were evident, likely due to the highly variable blood levels as increased pre-partum cortisol is intrinsic to parturition. Similarly, no treatment effect on sow PGFM concentrations was seen. Circulating PGFM levels reflect PGF₂ α biosynthesis and was used as a measure of prostaglandin-mediated inflammation (Ricciotti and FitzGerald 2011). However, a failure to detect a difference may reflect the short (15 min) half-life of PGFM and the need for more intensive sampling.

Data from the present experiment indicate a negative effect of anti-inflammatory drugs on subsequent reproductive performance, especially in the NSAID-treated sows. The aetiology of this effect is not known. However, it is possible that inhibition of prostaglandins impaired early uterine involution with adverse consequences for subsequent embryo survival in the next pregnancy. This is supported by the observation that prostaglandin analogue injected 24-48 h post farrowing increased the next litter size in older parity sows (Vanderhaeghe *et al.* 2008). This would also interact with farrowing hygiene as beneficial effects of post-partum prostaglandins are evident primarily in sow herds with ongoing poor performance likely associated with farrowing hygiene (Kirkwood 1999).

5. Conclusion

In conclusion, NSAID's should not be administered prior to farrowing for older parities as there is an increased risk of intra-partum piglet death, as well as poorer immunoglobulin uptake in the piglets. There was some indication that NSAIDs improved sow-wellbeing leading up to farrowing, and improved sow feed intake, but pre-partum anti-inflammatory injection does little to improve postnatal piglet survival or growth.

6. Limitations/Risks

Ideally, the anti-inflammatory administration would have been as close to farrowing as possible in order to have the highest impact on reducing pain and inflammation associated with parturition. The base-funded facility where the experiment was conducted did not routinely induce sows to farrow, but in order to

ensure appropriate timing of administration, the anti-inflammatory could have been given as part of an induction protocol. Or alternatively, in feed/water medication could have been tested.

7. Recommendations

As a result of the outcomes in this study the following recommendations have been made:

1. Injecting sows with a non-steroidal anti-inflammatory prior to farrowing reduced the number of piglets born alive, and impaired subsequent farrowing rates and so should be avoided.
2. Steroidal anti-inflammatory administration can be used to improve crated sow wellbeing as fewer facial injuries and improved feed intake were observed, but its use does not improve piglet survival and growth.

8. References

- Almeida, TF, Roizenblatt, S, Tufik, S (2004) Afferent pain pathways: a neuroanatomical review. *Brain Research* **1000**, 40-56.
- Antonucci, R, Zaffanello, M, Puxeddu, E, Porcella, A, Cuzzolin, L, Pilloni, MD, Fanos, V (2012) Use of non-steroidal anti-inflammatory drugs in pregnancy: impact on the fetus and newborn. *Current Drug Metabolism* **13**, 474-490.
- Challis, JRG, Berdusco, ETM, Jeffray, TM, Yang, K, Hammond, GL (1995) Corticosteroid-binding globulin (CBG) in fetal development. *The Journal of steroid biochemistry and molecular biology* **53**, 523-527.
- Douglas, AJ, Russell, JA (2001) Chapter 5 Endogenous opioid regulation of oxytocin and ACTH secretion during pregnancy and parturition. In 'Progress in Brain Research.' (Ed. AJDRJWCDI J.A. Russell.) Vol. Volume 133 pp. 67-82. (Elsevier:
- Farney, JK, Mamedova, LK, Coetzee, JF, Minton, JE, Hollis, LC, Bradford, BJ (2013) Sodium salicylate treatment in early lactation increases whole-lactation milk and milk fat yield in mature dairy cows. *Journal of Dairy Science* **96**, 7709-7718.
- Hausmann, M, Lay, D, Buchanan, H, Hopper, J (1999) Butorphanol tartrate acts to decrease sow activity, which could lead to reduced pig crushing. *Journal of Animal Science* **77**, 2054-2059.
- Huser, JS, Plush, KJ, Pitchford, WS, Kennett, TE, Lines, DS (2015) Neonatal split suckling improves survival of small piglets. *Animal Production Science* **55**, 1477-1477.
- Jarvis, S, McLean, K, Chirnside, J, Deans, L, Calvert, S, Molony, V, Lawrence, A (1997) Opioid-mediated changes in nociceptive threshold during pregnancy and parturition in the sow. *PAIN* **72**, 153-159.
- Jarvis, S, McLean, KA, Calvert, SK, Deans, LA, Chirnside, J, Lawrence, AB (1999) The responsiveness of sows to their piglets in relation to the length of parturition and the involvement of endogenous opioids. *Applied Animal Behaviour Science* **63**, 195-207.

- Loor, JJ, Dann, HM, Everts, RE, Oliveira, RFM, Green, CA, Guretzky, NAJ, Rodriguez-Zas, SL, Lewin, HA, Drackley, JK (2005) Temporal gene expression profiling of liver from periparturient dairy cows reveals complex adaptive mechanisms in hepatic function. *Physiological Genomics* **23**, 217-226.
- Mainau, E, Ruiz-de-la-Torre, JL, Dalmau, A, Salleras, JM, Manteca, X (2012) Effects of meloxicam (Metacam®) on post-farrowing sow behaviour and piglet performance. *animal* **6**, 494-501.
- Mainau, E, Temple, D, Manteca, X (2016) Experimental study on the effect of oral meloxicam administration in sows on pre-weaning mortality and growth and immunoglobulin G transfer to piglets. *Preventive Veterinary Medicine* **126**, 48-53.
- Manjarín, R, Montano, YA, Kirkwood, RN, Bennet, DC, Petrovski, KR (2018) Effect of piglet separation from dam at birth on colostrum uptake. *Canadian journal of veterinary research* **82**, 239-242.
- Mullins, CR, Mamedova, LK, Brouk, MJ, Moore, CE, Green, HB, Perfield, KL, Smith, JF, Harner, JP, Bradford, BJ (2012) Effects of monensin on metabolic parameters, feeding behavior, and productivity of transition dairy cows. *Journal of Dairy Science* **95**, 1323-1336.
- Nowland, TL, van Wettene, WHEJ, Plush, KJ (2017) Confinement of sows at parturition increases the incidence of behaviours thought to indicate pain. *Animal Production Science* **57**, 2444-2444.
- Petersson, M, Alster, P, Lundeberg, T, Uvnäs-Moberg, K (1996) Oxytocin increases nociceptive thresholds in a long-term perspective in female and male rats. *Neuroscience Letters* **212**, 87-90.
- Ricciotti, E, FitzGerald, GA (2011) Prostaglandins and Inflammation. *Arteriosclerosis, thrombosis, and vascular biology* **31**, 986-1000.
- Simmons, DL, Botting, RM, Hla, T (2004) Cyclooxygenase isozymes: The biology of prostaglandin synthesis and inhibition. *Pharmacological Reviews* **56**, 387-437.
- Tenbergen, R, Friendship, R, Cassar, G, Amezcua, MR, Haley, D (2014) Investigation of the use of meloxicam post farrowing for improving sow performance and reducing pain. *Journal of Swine Health and Production* **22**, 10-15.
- Vanderhaeghe, C, Dewulf, J, Daems, A, Van Soom, A, de Kruif, A, Maes, D (2008) Influence of postpartum cloprostenol treatment in sows on subsequent reproductive performance under field conditions. *Reproduction in Domestic Animals* **43**, 484-489.
- Viitasaari, E, Hanninen, L, Heinonen, M, Raekallio, M, Orro, T, Peltoniemi, O, Valros, A (2013) Effects of post-partum administration of ketoprofen on sow health and piglet growth. *Veterinary Journal* **198**, 153-157.
- Viitasaari, E, Raekallio, M, Heinonen, M, Valros, A, Peltoniemi, O, Hänninen, L (2014) The effect of ketoprofen on post-partum behaviour in sows. *Applied Animal Behaviour Science* **158**, 16-22.