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Systemic inflammatory response and lack of preventive effect of post-partum pain medication with ketoprofen on shoulder ulcers of sows

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Abstract

Shoulder lesions are common in lactating sows and can affect their welfare. We assessed the systemic inflammatory response to shoulder ulcers and monitored the preventive effect of post-partum administration with non-steroidal anti-inflammatory medication (ketoprofen) on their prevalence. In a double-blind placebo-controlled field trial, 144 YxL hybrid sows farrowing in crates with a cast-iron floor received either ketoprofen (3 mg/kg) or placebo as an intramuscular injection on days 0-1 after parturition. During the lactation period (weeks 1-4) all sows were assessed weekly for the presence of shoulder ulcers (0 = no ulcer, 1 = unilateral ulcer, 2 = bilateral ulcers; in all cases at least epithelial damage). From a subset of 37 sows, haptoglobin (Hp), albumin (ALB) and cortisol (COR) were measured from blood samples taken 10 to 12 days after farrowing. Results were analyzed according to a linear regression model for associations between Hp, ALB, COR and shoulder ulcers. A random ordered logistic model was used to assess risk factors (body condition score (BCS), back and shoulder fat, decrease in BCS or fat layer thickness during lactation, parity, number of live born and stillborn piglets, piglets weaned, shoulder ulcer scar) and the effect of ketoprofen treatment. Total prevalence of shoulder ulcers at lactation weeks 1-4 was 26.4%, 33.3%, 38.2% and 38.9%, respectively. Prevalences of unilateral shoulder ulcers at lactation weeks 1-4 were 16.7%, 19.4%, 20.8% and 18.8%, and prevalences of bilateral shoulder ulcers were 9.7%, 13.9%, 17.4%, and 20.1%. There was a decrease in albumin and an increase in Hp levels in sows with bilateral shoulder ulcers compared with sows without shoulder ulcers ($P < 0.001$) or unilateral shoulder ulcers ($P = 0.014$ for ALB, $P = 0.021$ for Hp). Changes in COR levels were not statistically significant but sows with bilateral shoulder ulcers tended to have lower cortisol levels than sows without ulcers ($P = 0.061$) and sows with unilateral shoulder ulcers ($P = 0.089$). Ketoprofen failed to protect against shoulder ulcers, but instead the treated sows had an increased number of shoulder lesions at the second and third lactation week ($P = 0.023$ and $P = 0.049$). Previous shoulder ulcer was a predisposing factor for shoulder ulcers at all lactation weeks ($P < 0.001$). Higher body condition score (BCS) and a thicker back and shoulder fat layer protected against shoulder ulcers. The results indicate that bilateral shoulder ulcers trigger a systemic response and should therefore be regarded as a significant finding in clinical evaluation. Postpartum administration of ketoprofen was ineffective in shoulder ulcer prevention.

Keywords: sow, shoulder ulcer, ketoprofen, systemic response, welfare

Introduction

A shoulder ulcer of a lactating sow represents necrotic tissue damage of the skin and subcutaneous tissue (Herskin et al., 2011). In previous studies, most from more than 10 years ago, the prevalence of shoulder ulcers has been estimated to be 10-34%, with substantial variation among herds (Bonde et al., 2004; Cleveland-Nielsen et al., 2004a, 2004b; KilBride et al., 2009a; Zurbrigg, 2006). Shoulder ulcers are caused by long periods of pressure associated with prolonged recumbency, and are partly comparable to human pressure ulcers (Jensen, 2009). During farrowing and early lactation, a sow spends long periods of time lying on her side, thus placing a great proportion of her body weight on the shoulder (Hötzel et al., 2004). This behavior is influenced not only by the health status of the sow (Bonde et al., 2004), but also by environmental factors, such as room temperature (Malmkvist et al., 2012), availability of bedding (Damm et al., 2003), and whether the sow is kept in a crate or in a loose-housing pen (Blackshaw et al., 1994; Cronin et al., 1996). Davies et al. (1997) suspected that periparturient conditions, especially patterns of recumbency and sow activity during farrowing and early lactation, affect the development of shoulder ulcers. Predisposing factors for shoulder ulcers include body condition, back fat thickness, presence of a scar from a previous shoulder ulcer and flooring (Herskin et al., 2011; KilBride et al., 2009a).

Shoulder ulcers vary greatly in severity. They develop as a progressive process, from ´top to bottom´, with lesions appearing first in the skin. Necrotic tissue lesions are found in all stages of shoulder ulcers, and in the most advanced form of shoulder ulcer the underlying bone (*tuber spina* scapulae) is exposed and deformed (Jensen, 2009). Though clear variation in lesion severity is often clinically evident, a reliable classification system for shoulder ulcers *ante mortem* has been difficult to formulate.

Shoulder ulcers are likely to cause pain and impact sow welfare (Dahl-Pedersen et al., 2013; Larsen et al., 2015). However, there is a lack of scientific data on the level of pain and inflammatory responses related to shoulder ulcers (Herskin et al., 2011). Shoulder ulcers can cause extensive tissue lesions with necrosis and inflammation (Jensen et al., 2014). Tissue inflammation or infection causes a local tissue response that is represented with a release of cytokines and, as a consequence, acute inflammatory response (Chen et al., 2003; Wang et al., 2001). As part of the acute phase response, haptoglobin (Hp) is a well-established marker of tissue damage in pigs (Heinonen et al., 2010; Petersen et al., 2002). Hp production is mainly regulated by cytokine levels, and their levels correlate with the extent of tissue damage (Chen et al., 2003). In addition, Hp levels can increase also as a consequence of physiological stress (Murata et al., 2004). Thus, as a measurable marker of

inflammation and stress, Hp can even act as a welfare indicator (Chen et al., 2003; Eckersall, 2000; Murata et al., 2004; Piñeiro et al., 2007; Salamano et al., 2008).

Low albumin (ALB) levels in humans undergoing surgery, as studied by Lindgren et al. (2005), represent a risk factor for pressure ulcers. In addition, Ek et al. (1991) showed that as a part of nutritional status assessment, low ALB levels were related to a higher risk of pressure ulcer in humans. The reason for the correlation between serum ALB levels and pressure ulcers is unclear (Anthony et al., 2000). According to Ek et al. (1991), odema caused by low ALB levels could lead to microcirculatory changes, and thus increase the risk for pressure ulcers. In pigs, ALB functions as a negative acute phase protein, decreasing at the time of infection (Lampreave et al., 1994). Accordingly, a correlation with shoulder ulcers can also be expected in sows. To our knowledge, association of ALB levels with shoulder ulcers in sows has never been studied.

Cortisol (COR) is a traditionally used and widely researched marker of stress in various species. Higher COR levels represent the activation of hypothalamic-pituitary-adrenal (HPA) axis, which can be induced by a large variety of disturbances in metabolic homeostasis, such as physiological stress (Mormède et al., 2007). COR levels may correlate with Hp levels, reflecting different manifestations of stress response in pigs (Ott et al., 2014). Furthermore, COR levels can increase as a response to immunological stress, along with blood cytokine levels (Webel et al., 1997). In sows with shoulder ulcers, increase in cortisol levels can be expected both due to physiological stress (pain and discomfort) and local tissue changes (necrosis and inflammation), and thus data about salivary cortisol concentration in addition to plasma Hp levels would help to estimate the systemic response to shoulder ulcers of varying severity.

One type of pain-related behavior in animals is inactivity (Roughan and Flecknell, 2000; Short, 1998). In sows, inactive lateral lying bouts cause external pressure on the shoulder tissues, decreasing the blood flow and leading to tissue hypoxia and thrombosis (Lowthian, 2005; Vande Berg and Rudolph, 1995). The longest uninterrupted lying bouts have been shown to occur at the second day of lactation (Rolandsdotter et al., 2009), and shoulder ulcers can start to develop during the first two days of lactation (Davies et al., 1996; Rolandsdotter et al., 2009). In shoulder ulcer prevention, minimizing the duration of external pressure therefore seems essential. With administration of NSAID, we could provide pain relief and thus prevent pain-related inactivity, which could decrease prolonged, uninterrupted lateral recumbency. Concurrently, appetite would be maintained and lactation-related decrease in BCS and back fat thickness would accordingly be reduced (Viitasaari et al., 2013; Weary et al., 2009). Ketoprofen is an NSAID belonging to the arylproprionic acid group. It has analgesic,

anti-inflammatory and antipyretic activities, and is thus indicated in pigs within European Union for respiratory infections and Mastitis-Metritis-Agalactia (MMA) syndrome (Committee for Veterinary Medicinal Products, 1996). Ketoprofen decreases the biosynthesis of peripheral prostaglandins by inhibiting cycle-oxygenase enzymes, which has been considered to explain the analgesic effects of ketoprofen (Kantor, 1986). However, also central mechanisms of analgesia from ketoprofen have been shown (Cashman, 1996; Wilier et al., 1989).

We hypothesized that shoulder ulcers could be prevented by administration of NSAID, that would relieve pain associated with farrowing and early lactation. We used ketoprofen, based on practical availability and evidence of efficacy in sows (Mustonen et al., 2011). Our additional goal was to assess the systemic response to shoulder ulcers by monitoring Hp, ALB, and COR levels 10-12 days after farrowing, when the development of shoulder ulcers had progressed (Davies et al., 1997).

Materials and methods

Animals and housing

Our study took place on a Finnish piglet-producing farm with 400 Yorkshire x Landrace first-generation hybrid sows. The farm has a high health status and is clinically free of enzootic pneumonia, salmonellosis, PRRS, swine dysentery (*Brachyspira hyodysenteriae*) and mange (*Sarcoptes scabiei* var. *suis*). Data were collected during one calendar year, and the study was completed in 2012. During gestation, the sows were kept in gestation pens, in groups of 5 to 7 individuals. The pens contained a resting area (3.5 m^2/sow) with a deep bedding of peat (about 0.5 m deep) and a feeding area with a concrete floor. Approximately one week (5-8 days) before expected farrowing, the sows were moved into a conventional farrowing pen with a closed farrowing crate and a slatted floor. The farrowing crate (width 0.6-0.7 m, length 2.4 m) had a partly slatted cast-iron floor (total width 0.63 m, total length 1.96 m). The floor under the sow had a more solid area (length 97cm) at the front part of the crate, with approximately 10% of the floor surface slatted. The floor under the front part of the sow is shown in Figure 1. For the piglets the pen had a plastic fully-slatted floor with solid heat plates (width 0.4 m, length 0.6 m). Sows were provided with a handful of hay or straw daily as rooting material, piglets with peat and paper roughage. Sows were fed three times daily (at 7:00, 12:00 and 17:00 h) with commercial feed (Emakko-Pekoni®, Suomen Rehu, FINLAND, NE 12.05 MJ/kg, crude protein 15.5%, 2-2.9 kg/day). Water was freely available from a drinking nipple, minimum flow of 4 liters / minute. From one week of age the piglets were provided with commercial piglet feed (Junior-

Nasu®, Suomen Rehu, FINLAND) for ad libitum intake. The room temperature of each farrowing unit was recorded on a weekly basis (digital temperature probes, in-build farm system). Average ambient temperature (all groups, all lactation weeks) was 22.9°C, with a range of 21.1-25.4°C. Piglets were weaned at 4 weeks (average age 25 days; minimum 19 days, maximum 29 days). At weaning, the sows were moved into insemination crates with a concrete floor for heat detection and insemination, and kept in the crates for 3 to 4 weeks, until pregnancy was verified. The Finnish National Animal Experiment Board (ESAVI/3331/04.10.03/2011) approved the study protocol.

Study design

We performed a double-blind, placebo-controlled clinical field trial. The study included all farm sows expected to farrow at the time of the study, excluding those that showed signs of systemic illness (apathy, lameness, decreased appetite) in prepartum clinical assessment. In total, 153 sows (20 first parity, 133 second or greater parity) were included in the study. The calculated sample size was 70 in each treatment group (placebo and ketoprofen). Calculations were based on the hypothesis that differences in shoulder ulcer (unilateral or bilateral) prevalence between control and ketoprofen groups were at least 25% (two-sided P level at 0.05 and a study power of 80%). Sows were divided based on their expected farrowing date into ten farrowing batches with batch size ranging from 11-18 sows (average 14). The division of sows into farrowing batches was done according to the usual practice of the farm, with no influence from the study plan. Results from nine sows were excluded from the analysis because of missing data. Of those nine sows, three from the ketoprofen group died due to unknown cause during the study: one sow from batch 6 at lactation week 2 and two sows from batch 8 at lactation weeks 1 and 4. Six sows, four from ketoprofen group and two from placebo, were relocated before the end of lactation, based on farm management that was not affected by the study plan. Of those sows, data were missing from the last (4^{th}) lactation week. On 3^{rd} lactation week, four of the sows did not have a shoulder ulcer, one had unilateral shoulder ulcer, and one had a bilateral shoulder ulcer.

Sows in each farrowing batch were randomly divided into two treatment groups (ketoprofen vs. placebo). Treatment group was marked with blue and red colored paper sheets (blue = ketoprofen and red = placebo). At batch randomization we had one paper sheet for each sow; half of the paper sheets for the batch were blue and half were red, and they were manually randomly mixed. After mixing, the paper sheets were randomly distributed to the sows in the batch, and treatment group was

thereafter indicated with a color-coded paper sheet on the farrowing crates. The farmer, who performed the medications according to the color codes, was blind to the medication group the sow had been allocated to.

Sows were medicated for two days with either ketoprofen (3 mg/kg bw, Ketovet 100 mg/mL, Richter Pharma AG, Austria) or placebo (isotonic saline), administered as an intramuscular injection in the neck, approximately 5 cm caudally from the ventral base of the ear. The first injection was given when the sow had farrowed or when the onset of farrowing was noted, between 07:30 to 16:00 h (normal working hours). The second injection was given during the same normal working hours, maintaining 24 hours between injections.

Assessment of the sows

All sows were examined approximately one week before expected farrowing (average 3 days, minimum 0 days, maximum 10 days), to measure the fat layer in the back and in the shoulder, to evaluate body condition score (BCS) and to assess shoulder ulcer scars. Scars were gauged on scale 0/1; 0 = no scar (healthy skin with no epithelial lesions or only lesions from a clearly different origin, for example fight marks), 1 = scar (epithelial lesion with thickening and visual evidence of fibrous connective tissue or granulation tissue in the skin on top of *tuber spina scapulae*) in one or in both shoulders. Assessments were performed blind regarding the medication group.

The fat layer measurements were performed with an ultrasonic measuring appliance (P2, Renco lean-meater®, Renco corporation, Minneapolis, USA). Back fat layer was measured at the level of the last rib, 6 cm to either side of the spine. The shoulder fat layer was measured from the left shoulder, above the *tuber spina scapulae,* 5 cm dorsally from the *acromion.* Measurement was performed on top of healthy skin, avoiding possible ulcer-, or scar-related tissue changes. During measurement, the sow was either standing or sitting.

The evaluation of the BCS was done manually, as described by Bonde et al. (2004), but with the modification of assigning also half points (scale from 1-5, with an accuracy of 0.5). BCSs were evaluated by two researchers, whose consistency and agreement were tested before the study.

During lactation weeks 1-3, all sows were assessed once weekly for shoulder ulcers, on a 0/1/2 scale (0 = no ulcer, 1 = unilateral ulcer with at least epithelial damage, 2 = bilateral ulcer with at least epithelial damage in both shoulders).

At weaning (lactation week 4), in addition to shoulder ulcer assessment as described for lactation weeks 1-3, back and shoulder fat measurements, and evaluation of BCS were repeated as before farrowing.

Farrowing information (parity, number of piglets born, number of piglets weaned) was recorded. Farm personnel recorded the number of live born and stillborn piglets based on their observations within routine farm management. Cross-fostering was performed within the first 24 hours after birth in order to match litter size with the number of functional teats. A newborn piglet was recorded as born still if lacking breathing and moving activity within 15 minutes of birth.

Acute phase proteins and cortisol

We took stratified blood samples from a subset of 37 sows, from three different farrowing batches. The stratification was based on previous randomization (ketoprofen /placepo). We aimed to take half of the sampled sows in each batch so that they were previously medicated with ketoprofen and the other half of them with placebo. In addition, sows were visually assessed for occurrence of shoulder ulcers at the time of the sampling. Those sows were then included based on presence of shoulder ulcers (shoulder ulcer score 0 / 1; 0 = no ulcer, 1 = uni- or bilateral ulcer), so that the samples would contain both scores on a 50%/50% basis. Samples were taken approximately 12 days after farrowing, with a range of 4 to 14 days (average 10.5 days, median 11 days). Variation in the sampling date originated from practical reasons, since the sows were assessed once weekly. Sampling time was the same for all groups, between feedings of 12:00 h and 17:00 h. Samples were taken from the coccygeal vein in the tail, with an open method into EDTA-tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), centrifuged (1 900 g, 15 minutes) and kept frozen (-18°C) until analysis.

The serum samples were analyzed for ALB, Hp, and COR. ALB was analyzed using a colorimetric method with an automated clinical biochemistry analyzer (Spotchem EZ SP-4430, Arkray, Kyoto, Japan), following the manufacturer's instructions for analysis of porcine serum. Hp was analyzed using a hemoglobin-binding method described for cows (Makimura and Suzuki, 1982). Tetramethylbenzidine was used as a chromogen (Alsemgeest et al., 1994), with a 5 µg sample volume (originally 20 µg). The assay results were read at 450 nm using a spectrophotometer (SUNRISE, Tecan, Männedorf, Switzerland). Pooled and lyophilized aliquots of porcine acute phase serum were used to create standard curves by serial dilutions. The standard was calibrated using a porcine serum

sample of known Hp concentration provided by the European Commission Concerted Action Project (number QLK5-CT-1999-0153). The standard curve range was 0.254-4.06 g/L. A commercially available RIA kit (Orion Diagnostica, Spectria®**,** Espoo, Finland, coated tube radioimmunoassay) was used with modifications to measure cortisol in porcine plasma. Analysis was done as previously validated for pigs by Oliviero et al. (2008).

Statistics

Linear regression models were used to explore different (no ulcers, unilateral ulcers, and bilateral ulcers) shoulder ulcer effects on the sow inflammatory response. Hp, albumin, and cortisol were included in those models as response variables. Models initially included sow variables (parity, piglets weaned, number of still born and live born piglets, sampling day interval from parturition to sampling day, BCS, back fat (mm), and shoulder fat (mm) before farrowing and at weaning), shoulder ulcers (no ulcers, unilateral ulcers, and bilateral ulcers), and farrowing group as explanatory variables. Backward elimination was performed for the final models. Farrowing group was retained in all models as a potential cofounding factor. The model assumptions were verified by scatter and normality plots of standardized residuals, and logarithmic transformation of Hp and square root transformation of cortisol were used.

A random-ordered logistic model was used to explore risk factors (BCS, back and shoulder fat, decrease in BCS or fat layer thickness during lactation, parity, number of live born and stillborn piglets, piglets weaned, shoulder ulcer scar) for shoulder ulcers and effects of ketoprofen treatment after farrowing on the presence of shoulder ulcers during lactation. An ordered logistic model was chosen because bilateral shoulder ulcers showed a clearly stronger inflammatory response (higher Hp and lower albumin) than unilateral ulcers, and an ordinary logistic model with two level response variables (ulcers yes or no) would have underestimated the severity of shoulder ulcers. For ordered logistic models, three levels of ordered dependent variables for shoulder ulcers were used (no ulcers, unilateral ulcers, and bilateral ulcers). As BCS, back fat and shoulder fat were highly correlated, their associations with shoulder ulcers were evaluated using separate models. To study the effect of the degree of body mass decrease during the lactation period on shoulder ulcers, BCS, back fat, and shoulder fat results at week four were decreased from prepartum results and used in models as predictive variables. Models initially included the following explanatory variables: sow variables (parity, live born and still born piglets, piglets weaned), ketoprofen treatment, presence of shoulder

ulcer scar prepartum, and one of body condition measured before farrowing (BCS as a four-level variable: < 3.0, = 3.0, = 3.5, and > 3.5, thickness of back fat in mm, and thickness of shoulder fat in mm) and decrease in body condition variables (BCS, thickness of back fat and thickness of shoulder fat separately) and all those variable interactions with lactation weeks as fixed factors. Sow was included as a random factor in all models to account for clustering effect. A backward elimination method was used for final models. For evaluating ketoprofen effect on shoulder ulcers, a model with BCS was used as a model with the most conservative association estimate between ulcers and ketoprofen treatment.

The underlying assumption of ordered logistic regression was that the relationship between each pair of outcome groups is the same (so-termed proportional odds assumption). Therefore, for a one-unit change in the predictor variable, the odds for cases in a group greater than the response variable level (versus one less than or equal to the level) are the proportional odds times larger. The proportional odds assumption for all models was tested using a likelihood ratio test and a Brant test. As all tests were non-significant, model assumptions were met. Significance level was set at $P \leq 0.05$ and P = 0.051-0.099 was interpreted as tendency. Results are expressed as means with ± standard deviation (SD) or least squared means (LSMeans) ± standard error (SE) and odds ratios (OR) with 95% confidence interval (CI).

STATA 11.0 (Stata Corporation, Texas, USA) software was used for all statistical analyses.

Results

Total prevalence of shoulder ulcers at lactation weeks 1-4 was 26.4%, 33.3%, 38.2% and 38.9%, respectively. Prevalences of unilateral and bilateral shoulder ulcers at lactation weeks 1-4 were 16.7%, 19.4%, 20.8%, 18.8% and 9.7%, 13.9%, 17.4%, 20.1%, respectively. Prevalences by study groups and lactation weeks are given in Figure 2. Scars from shoulder ulcers in previous lactation periods were evident in 45.1% of the sows. Mean and SD of sow parity, number of live born and stillborn piglets, number of weaned piglets, BCS, thickness of back and shoulder fat layer by study groups are given in Table 1.

Ketoprofen failed to protect against shoulder ulcers (Table 2). There was no significant association between ketoprofen treatment and shoulder ulcers at the first week after parturition. At lactation week two and three, ketoprofen treated sows were predisposed to shoulder ulcers (OR 2.86, 95% CI: 1.15-

7.09; P = 0.023 and OR 2.33, 95% CI: 1.00-5.41; P = 0.049). Number of stillborn piglets increased the risk of shoulder ulcers at lactation weeks two and four (P = 0.033 and P = 0.025; Table 2). Previous shoulder ulcer (ulcer scar) was a predisposing factor for shoulder ulcers at all lactation weeks (P < 0.001; Table 2). Protective factors were higher BCS (P < 0.001; Table 2), thicker back fat layer (P < 0.001 at all lactation weeks; mean and SD are given in Table 3), and thicker shoulder fat layer (P < 0.001 at all lactation weeks; mean and SD are given in Table 3).

Serum Hp (Figure 3) was significantly higher (P < 0.001) and serum ALB (Figure 4) was significantly lower (P = 0.001) in sows with bilateral shoulder ulcers than in sows with no shoulder ulcers. Furthermore, serum Hp was higher (P = 0.021) and serum ALB was lower (P = 0.014) in sows with bilateral shoulder ulcers compared with sows with a unilateral shoulder ulcer. There was a tendency of lower cortisol concentrations in sows with bilateral ulcers than in sows without ulcers (P = 0.061) and between sows with bilateral ulcers than in sows with unilateral ulcers (P = 0.089). Between sows with no shoulder ulcer and a unilateral shoulder ulcer, there was no significant difference in serum Hp, ALB or COR levels.

Parity, number of live born piglets, number of weaned piglets, or decrease in body condition variables (decrease from prepartum values to fourth lactation week values for BCS, back fat layer, or shoulder fat layer, Table 2) were unrelated to the prevalence of shoulder ulcers at any lactation week.

Discussion

We failed to demonstrate a protective effect against shoulder ulcers from post-partum NSAID (ketoprofen) medication. Instead of a protective effect, our results indicated that ketoprofen treatment predisposes a sow to shoulder ulcers. This unexpected finding was, however, evident only during the second and third week of lactation. Viitasaari et al. (2013) reported that sows medicated with ketoprofen for 3 days after farrowing showed a slower shoulder ulcer deterioration 4 to 6 days postpartum, when compared with sows treated with saline placebo. We did not assess the daily change in shoulder ulcer score. However, Viitasaari et al. (2013) demonstrated that ketoprofen is unable to prevent the development of shoulder ulcers; at most it slows down the progression of the condition. Ketoprofen may alter pain-related behavioral response in sows, with variation in sows of different parity (Viitasaari et al., 2014). It is possible that NSAID medication enables pain to be ignored, and thus allows prolonged lateral recumbency, which could explain the predisposing effect of ketoprofen.

We established a predisposing effect on shoulder ulcers at lactation weeks 2 and 4 from an increased number of stillborn piglets. This is supported by Davies et al. (1997), who found a tendency of association between number of stillborn piglets and shoulder ulcer prevalence. Moreover, they recorded a similar positive correlation with shoulder ulcer severity. Number of stillborn piglets is positively correlated with farrowing duration (Björkman et al., 2017; Oliviero et al., 2010; Van Dijk et al., 2005). Farrowing duration, especially when increasing the duration of uninterrupted lying bouts, could affect the development of shoulder ulcers (Davies et al., 1996; Rolandsdotter et al., 2009). Stillborn piglets could also reflect other health issues that would increase the risk of developing shoulder ulcers, but in our study, this was not supported by clinical examination of the sows. Although reasons for the correlation of shoulder ulcers and the number of stillborn piglets are unclear, in shoulder ulcer prevention sows with increased numbers of stillborn piglets should receive more attention and enhanced preventive treatment.

Studies addressing shoulder ulcer treatment are rare, and they mainly assess the use of rubber mats or local ulcer treatment, once the shoulder ulcer has developed. In practical evaluation, efficient treatment methods have been difficult to find. Zurbrigg (2006) reported a faster recovery from shoulder ulcers in sows with a rubber mat placed on the floor of the farrowing crate. Furthermore, Kaiser et al. (2013) found a positive treatment effect from rubber mat and local treatment with zinc ointment. With careful planning (Schubbert et al., 2014), rubber mats could also be useful in shoulder ulcer prevention. But, due to the multifactorial nature of shoulder ulcers, other preventive methods should also be actively established. Even though ketoprofen was ineffective as a preventive medication against shoulder ulcers, we believe that sows with health issues requiring analgesia (such as lameness, MMA or prolonged farrowing) can benefit from appropriate ketoprofen medication. This assessment is based both on practical evaluation and findings by Viitasaari et al. (2013).

Shoulder ulcer prevalences at lactation weeks 1-4 were consistent with numbers reported in the literature (Herskin et al., 2011). Davies et al. (1996) reported much lower prevalence (8.3%) when all sows in a breeding herd, regardless of their time of farrowing, were assessed. But, they also reported that at the time of peak prevalence (11-20 days after farrowing), shoulder ulcers were found in up to 51% of the sows. Similar results were reported by Davies et al. (1997), with 12 days after farrowing shoulder ulcer prevalence reaching 48%. In our study, unilateral shoulder ulcer prevalence decreased by the fourth lactation week, which is in line with previous findings on shoulder ulcer healing already during lactation (Davies et al., 1997; KilBride et al., 2009b). Instead, the prevalence of bilateral shoulder ulcers increased throughout the lactation from 9.7% to 20.1%. Comparable

356 results on bilateral shoulder ulcer prevalence during lactation are difficult to find; Rolandsdotter et
357 al. (2009) reported that 6/18 sows (33%) had bilateral shoulder ulcers at the time of weaning.

358 The prevalence of shoulder ulcer scars, reflecting shoulder ulcers from previous lactations, was
359 45,1%. This is considered to be relatively high, although scar prevalence is rarely reported. Davies et
360 al. (1996) described that before farrowing approximately one quarter of sows had shoulder ulcer scars.
361 To date we have limited information about the healing process of shoulder ulcers. Healing within a
362 few weeks after weaning, even without treatment, is considered normal, but there seems to be large
363 variance in the duration and characteristics of the healing process, and the most prominent type of
364 healing occurs via secondary healing (Herskin et al., 2011). The high prevalence of shoulder ulcer
365 scars in our study might be due to a cumulative effect: previous shoulder ulcer predisposes a sow to
366 shoulder ulcers at subsequent lactations. Scars may also represent a poor healing process because
367 treatment of shoulder ulcers was rare on our study farm. Preventive methods, such as optimizing body
368 condition score and use of rubber mats, should be actively implemented on subsequent lactations to
369 sows with shoulder ulcer scars.

370 Shoulder ulcer prevalence has shown extensive herd related variation (Herskin et al., 2011). In
371 combination with the relatively high prevalence of shoulder ulcers in our study, the high prevalence
372 of scars from previous shoulder ulcers might suggest a herd-related management challenge, despite
373 good general herd health. In general, our study suggests that shoulder ulcers are an active health issue
374 in the pig industry, with at best moderate decrease in prevalence during the recent decade.

375 Our results showed that bilateral shoulder lesions triggered a systemic inflammatory response in
376 sows. This response was characterized by an increase in Hp and decrease in ALB concentrations,
377 when compared to sows with unilateral shoulder ulcer or absence of ulcers. As a consequence of
378 tissue damage, this reflects previous tail biting findings by Heinonen et al. (2010), who established a
379 positive correlation between Hp levels and tail biting lesion severity. Correlation of systemic
380 inflammatory response and the severity of unilateral or bilateral shoulder ulcer requires further study.
381 To date, division between unilateral and bilateral shoulder ulcers is included in some studies, but this
382 division is rarely compared with the severity of the lesions. As an exception, Davies et al. (1996)
383 reported that sows with bilateral shoulder ulcers had wider lesions than sows with unilateral lesions.

384 Hp levels are mainly regulated by cytokines, that are also active in the cellular level pain transduction
385 process (Kidd and Urban, 2001). Thus, elevated Hp levels leading to the activation of pain stimulus
386 pathways represents a logical consequence. Behavioral observations support this expectation of pain:

Larsen et al. (2015) found that sows with shoulder ulcers showed altered behavior and decreased maternal behavior, and shoulder ulcers were likely to cause pain. Therefore, even though welfare aspects of shoulder ulcers have been debated, the present study supports the assumption of endangered welfare in sows with shoulder ulcers.

In addition to Hp, lower ALB levels are considered to represent the inflammatory response as a negative acute phase protein (Lampreave et al., 1994). However, we were unable to locate information about ALB levels in sows as part of the acute phase response, especially when linked to shoulder lesions. There might also be additional reasons for the negative correlation between bilateral shoulder ulcers and albumin levels, such as nutritional aspects. Low albumin levels in humans can lead to loss of blood oncotic pressure and tissue odema, thus increasing the risk for pressure-related ulcers (Ek et al., 1991). Since odema is usually the result of severe hypoalbuminemia (Tulassay et al., 1989), this mechanism should not exert a major influence on our results. Albumin loss through large wounds is an acknowledged problem in humans (Lehnhardt et al., 2005), and could lead to a decrease in blood albumin levels, but we consider this to be a less likely explanation for our findings.

Our findings emphasize the clinical relevance of shoulder ulcers, especially regarding welfare. In line with increased attention towards shoulder ulcers, some countries have tightened the legislation concerning shoulder ulcers, and have set limitations on transportation of sows with shoulder ulcers wider than 3 cm (Barington et al., 2016). In addition, in Denmark sows with shoulder ulcers that involve the subcutaneous tissue can be handled as forensic cases (Barington et al., 2016). Based on systemic inflammatory response, bilateral shoulder ulcers should receive increased attention in treatment choices as well as in the general health assessment of sows. Furthermore, sows with bilateral shoulder ulcers should be assessed as possibly systemically ill, both in farm management and the food production chain. Inflammatory response in relation to shoulder ulcers has not been studied before, and the exact pathogenesis behind this reaction requires further assessment. Many factors can affect the systemic inflammatory response, such as inflammation, tissue trauma, stress and infection (Murata et al., 2004). Although infection in shoulder ulcers is intermittently considered a rare consequence, Lund et al. (2003) reported an infection accompanying up to 85% of shoulder ulcers. We did not study the infection rate of shoulder ulcers in our study. Systemic inflammatory response and its relation to shoulder ulcers, especially regarding lesion severity and time from farrowing, should be studied in more detail for better assessment of the extent of systemic response. It also seems clear that in both statistical and clinical evaluation, unilateral and bilateral shoulder ulcers should be assessed as separate entities.

Consistent with many previous studies, our study revealed that high BCS protects from shoulder ulcers. The same protective effect from a thicker back and shoulder fat layer was found. These protective effects were apparent in the first week of lactation. Thus, maintaining a BCS above 3.5 before farrowing is vital for preventing the development of shoulder ulcers.

Conclusions

Shoulder ulcers should be assessed as a condition with possible systemic effects, emphasizing the relevance of bilateral shoulder ulcers in clinical evaluation. Based on current knowledge and our results, the BCS and shoulder fat layer of sows represent an important intrinsic factor affecting the development of shoulder ulcers, with strong predisposing effect from a previous shoulder ulcer. Administration of NSAID in the immediate post-partum period was ineffective for preventing shoulder ulcers.

Conflict of interest statement

Fieldwork was funded by the Mercedes Zachariassen Foundation. The medications used in the study were funded by the pharmaceutical company Vetcare Oy. Data analyses were funded by the Finnish Ministry of Agriculture and Forestry. None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Figure 1. Partly-slatted cast-iron floor in the farrowing crate of the 153 study sows evaluated for shoulder ulcers, showing the floor in the front part of the farrowing crate, with approximately 10% of the floor surface slatted.

Figure 2. The prevalence of sows with shoulder ulcers (0 = no ulcers, 1 = unilateral ulcers, 2 = bilateral ulcers) in 144 sows treated with ketoprofen (n = 71) and with placebo (n = 73) by lactation week. Numbers over columns represent number of sows in ketoprofen/placebo group respectively.

* Significant (P = 0.023) predisposing effect of ketoprofen evaluated by random-ordered logistic model where three level shoulder ulcer groups as ordered categorical variable was used as response variable.

Significant (P = 0.049) predisposing effect of ketoprofen evaluated by random-ordered logistic model where three level shoulder ulcer groups as ordered categorical variable was used as response variable.

Figure 3. Sow serum haptoglobin (Hp) concentrations evaluated by regression according to shoulder ulcer groups (no ulcers, n = 22; unilateral ulcers, n = 9; and bilateral ulcers, n = 6) in 37 sows 4-14 after farrowing. The graph shows back-transformed (from logarithmic scale) least squared means (g/L, LSMeans) and standard errors (SE).

Figure 4. Sow serum albumin (ALB) concentrations evaluated by regression according to shoulder ulcer groups (no ulcers (n = 22), unilateral ulcers (n = 9) and bilateral ulcers (n = 6)) in 37 sows 4-14 after farrowing. The graph shows least squared means (g/L, LSMeans) and standard errors (SE).

633 **Table 1.** Sow parity, number of live born and stillborn piglets, number of weaned piglets, body
634 condition score (BCS), thickness of back and shoulder fat layer by treatment group (placebo or
635 ketoprofen) before farrowing (prepartum) and at weaning (postpartum).

Variable	Placebo (n = 73)		Ketoprofen (n = 71)	
	Prepartum (mean ± SD)	**Postpartum/ at weaning (mean ± SD)**	**Prepartum (mean ± SD)**	**Postpartum/ at weaning (mean ± SD)**
Parity		4.7 ± 3.1		4.8 ± 3.4
Weaned piglets		10.4 ± 2.1		9.8 ± 2.3
Live born piglets		10.6 ± 4.5		10.7 ± 4.4
Still born piglets		2.2 ± 2.2		1.9 ± 2.2
BCS	3.5 ± 0.8	3.2 ± 0.7	3.4 ± 0.7	3.0 ± 0.6
Back fat, mm	17.3 ± 5.6	13.7 ± 4.6	15.6 ± 5.1	12.5 ± 3.9
Shoulder fat, mm	17.3 ± 4.9	13.5 ± 3.7	16.0 ± 4.4	12.9 ± 3.2

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Table 2. Associations of sow risk factors (number of stillborn piglets and presence of shoulder ulcer scar before farrowing), body condition score (BCS) and ketoprofen treatment 0-1 days post partum (3 mg/kg, IM, 1x day, 2 days) with presence of shoulder ulcers (no ulcers, unilateral ulcers or bilateral ulcers) in sows (n = 144) by lactation weeks (1-4). Associations were tested using ordered logistic regression model.

Variables	OR[1]	95% CI of OR	P-value	Wald test P-value
Week 1 (n = 106/24/14)[2]				
Treatment group:				
placebo (n = 73)	1			
ketoprofen (n = 71)	1.66	0.65; 4.25	0.288	
Number of still born piglets	1.14	0.91; 1.42	0.255	
Ulcer scar[3]:				
no (n = 104)	1			
yes (n = 40)	9.67	3.25; 27.92	<0.001	
BCS[4]:				<0.001
<3.0 (n = 24)	1			
=3.0 (n = 35)	1.14	0.36; 3.11	0.912	
=3.5 (n = 33)	0.03	0.00; 0.23	0.001	
>3.5 (n = 52)	0.04	0.01; 0.16	<0.001	
Week 2[5] (n = 96/28/20)[2]				
Treatment group:				
placebo	1			
ketoprofen	2.86	1.15; 7.09	0.023	
Number of still born piglets	1.28	1.02; 1.61	0.033	
Ulcer scars:				
no	1			
yes	9.067	3.39; 24.16	<0.001	
BCS:				<0.001
<3.0	1			
=3.0	0.55	0.19; 1.62	0.277	
=3.5	0.02	0.00; 0.12	<0.001	
>3.5	0.02	0.00; 0.08	<0.001	
Week 3[5] (n = 89/30/25)[2]				
Treatment group:				
placebo	1			
ketoprofen	2.33	1.00; 5.41	0.049	
Number of still born piglets	1.16	0.94; 1.43	0.154	
Ulcer scars:				
no	1			
yes	11.62	4.62; 29.21	<0.001	
BCS:				
<3.0	1			<0.001
=3.0	0.37	0.12; 1.08	0.070	
=3.5	0.03	0.01; 0.12	<0.001	
>3.5	0.04	0.01; 0.14	<0.001	
Week 4 (n = 88/27/29)[2]				

Treatment group:				
placebo	1			
ketoprofen	1.84	0.82; 4.14	0.141	
Number of still born piglets	1.26	1.02; 1.53	0.025	
Ulcer scars:				
no	1			
yes	8.51	3.51; 20.61	<0.001	
BCS:				
<3.0	1			<0.001
=3.0	0.47	0.16; 1.37	0.167	
=3.5	0.03	0.01; 0.15	<0.001	
>3.5	0.06	0.02; 0.19	<0.001	

[1] Odds ratios from ordered logistic regression models (three level ordered response variable – no ulcers, unilateral ulcers or bilateral ulcers) implies that one unit change in the predictor variable, the odds for cases in a group that is greater than response variable level versus less than or equal to this level are the proportional odds times larger.

[2] Number of sows with no ulcers / unilateral ulcers / bilateral ulcers.

[3] Occurrence of previous shoulder ulcer.

[4] Body condition score before farrowing.

[5] Number of sows in different variables groups are the same as in lactation week 1.

Table 3. Sows body condition score (BCS), back fat and shoulder fat data (mean ± SD) by shoulder ulcer group (0 = no ulcer, 1 = unilateral ulcer, 2 = bilateral ulcer) and by lactation week (1-4).

Shoulder ulcer group	**Prepartum (mean ± SD)**			**At weaning (mean ± SD)**		
	0	**1**	**2**	**0**	**1**	**2**
Week 1 (n of sows)	106	24	14	106	24	14
BCS	3.6 ± 0.7	2.9 ± 0.6	2.6 ± 0.6	3.2 ± 0.6	2.7 ± 0.6	2.8 ± 0.6
Back fat, mm	17.9 ± 4.6	13.8 ± 3.6	12.4 ± 3.4	14.2 ± 3.1	10.8 ± 2.4	10.1 ± 2.4
Shoulder fat, mm	17.9 ± 5.2	12.8 ± 4.2	12.6 ± 4.5	14.4 ± 4.0	9.4 ± 2.5	10.1 ± 3.6
Week 2 (n of sows)	96	28	20	96	28	20
BCS	3.7 ± 0.7	3.1 ± 0.5	2.7 ± 0.6	3.3 ± 0.6	2.7 ± 0.6	2.7 ± 0.6
Back fat, mm	18.1 ± 4.6	14.8 ± 3.4	12.4 ± 3.5	14.5 ± 3.0	10.5 ± 2.8	10.8 ± 2.8
Shoulder fat, mm	18.4 ± 5.1	13.3 ± 4.0	12.2 ± 4.0	14.7 ± 3.9	10.2 ± 3.4	9.6 ± 2.9
Week 3 (n of sows)	89	30	25	89	30	25
BCS	3.7 ± 0.7	3.2 ± 0.6	2.8 ± 0.7	3.3 ± 0.6	2.8 ± 0.6	2.7 ± 0.6
Back fat, mm	18.1 ± 4.7	15.7 ± 4.0	12.9 ± 3.4	14.6 ± 3.1	11.3 ± 2.8	10.7 ± 2.9
Shoulder fat, mm	18.4 ± 5.2	14.0 ± 4.3	12.6 ± 4.1	14.8 ± 4.0	10.8 ± 3.2	10.0 ± 3.5
Week 4 (n of sows)	88	27	29	88	27	29
BCS	3.7 ± 0.7	3.1 ± 0.6	2.9 ± 0.7	3.3 ± 0.6	2.7 ± 0.5	2.8 ± 0.6
Back fat, mm	17.7 ± 4.7	16.2 ± 4.7	13.9 ± 4.0	14.5 ± 3.2	11.3 ± 2.9	11.0 ± 2.8
Shoulder fat, mm	18.1 ± 5.3	14.9 ± 4.9	13.1 ± 4.4	14.8 ± 4.0	10.5 ± 3.3	10.6 ± 3.5