Pain and Inflammation Management After Parturition in Dairy Cattle

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Calving is essential for both initiating lactation and producing the next generation of replacement heifers in dairy operations. However, the risk of damage to the soft tissues of the birth canal increases during labor (Sheldon et al., 2006), being even higher in cows that experience dystocic calvings (Farhoodi et al., 2000). It has been proposed that an initial, rapid and strong yet controlled inflammatory response after parturition is needed in order to allow for the physiological processes of placenta detachment and lochia removal, and eliminate uterine bacterial contamination, preventing uterine diseases and improving reproductive performance in dairy cows (LeBlanc, 2014). On the other hand, either an exacerbated or deficient immune response could lead to poor uterine involution and, consequently, the occurrence of uterine diseases (LeBlanc, 2014).

The parturition process is considered to be a painful and stressful event and, if proper management is not in place (e.g., nutrition, cow comfort), dairy cows can experience exacerbated inflammatory and metabolic disturbances that can lead to the impairment of cow performance and health. The levels of both haptoglobin, an acute-phase protein used to measure inflammation in cattle, and cortisol highly increase around calving and decrease days later (Comline et al., 1974; Uchida et al., 1993). Results from a recent study (Barragan et al., 2018; unpublished data) found that cows that experienced more than one health event during the first 60 days of lactation had higher concentrations of inflammatory and stress biomarkers during the first hours after parturition. This suggests that an exacerbated inflammatory response around calving may lead to an increased susceptibility to diseases in early lactation. For instance, cows that experienced subclinical and clinical hypocalcemia had higher concentrations of cortisol around calving compared to healthy animals (Goff and Horst, 1997). Similarly, cows that experienced metritis had higher concentrations of haptoglobin around calving compared to cows that did not (Huzzey et al., 2009).

During the peri-parturient period, cows experience some degree of metabolic stress caused by a physiological drop in dry matter intake; this forces them to mobilize body reserves, especially fat tissue (i.e., nonesterified fatty acid [NEFA], β-hydroxybutyrate [BHB]; Grummer, 1993). These fat tissue
metabolites, when excessive, can activate pro-inflammatory molecules that increase insulin resistance, thus magnifying the mobilization of body reserves (LeBlanc, 2014). Furthermore, high NEFA concentrations may also directly initiate an inflammatory cascade by activating inflammatory cells through the binding to toll-like receptors (LeBlanc, 2014).

Moreover, high concentrations of NEFA and BHB directly impair immune system functions, increasing the risk of metabolic and infectious diseases in dairy cattle during the early lactation period (LeBlanc, 2010, 2014). For instance, cows with high concentrations of NEFA (>0.5 mEq/L) and BHB (>1200 μmol/L) were 3.6 times and 8 times, respectively, more likely to have a DA compared to cows that were below these values (LeBlanc et al., 2005). Furthermore, neutrophils exposed to NEFA in vitro were less viable, and a greater proportion suffered necrosis compared to unexposed cells (Scalia et al., 2006), suggesting a decreased immune function and increased susceptibility to infectious diseases in dairy cows that experience high concentrations of these metabolites.

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, 2011). The IASP stated that “the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment” (IASP, 2011). Dairy cattle are not only unable to verbally communicate when they are experiencing pain, but are also prey animals that have evolved to express subtle pain-related behaviors in order to avoid being targeted by predators (Johnson, 2016). Therefore, assessing pain and discomfort in cattle can be challenging, and the levels of such are often underestimated. A recently proposed hormone used to assess pain in cattle is substance P (SP). SP is a neuropeptide mainly involved in pain transmission and modulation in the dorsal horn of the spinal cord (DeVane, 2001). Although this hormone has been found to be elevated in calves after dehorning and castration (Coetzee et al., 2008; Allen et al., 2013), it appears to remain constant after normal and difficult calvings in dairy cattle (Barragan, et al., 2017a). This might be explained due to the physiological pain modulation processes that take place during calving such as endogen opioid secretion (Mainau and Manteca, 2011), or due to the fact that calving is a relatively short-term event, while SP has been associated with more prolonged pain (Honoré et al., 1999).

In addition to the increased concentrations of pain, stress and inflammation hormones around calving, there are several behaviors associated with pain and discomfort that have been reported in cows during labor, such as decreased feeding and drinking frequency, looking back at the flank region, vocalization and restless behavior, among others (Berglund and Philipsson, 1987; Miedema et al., 2011;
Schuenemann et al., 2011; Jensen, 2012). Furthermore, the perception of pain among cattle practitioners, regarding cows undergoing common procedures and health disorders in production operations, may be high. For instance, in a survey performed in New Zealand, cattle practitioners categorized dystocia as a severely painful event, suggesting that practitioners are aware of the degree of pain cows experienced during difficult calving (Laven et al., 2009). However, only 34% of veterinarians provided analgesia following dystocic calvings (Hewson et al., 2007).

Currently, there are no drugs approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of pain in cattle (AABP, 2015). However, veterinarians can prescribe drugs for pain treatment in an extralabel (ELDU) manner (AVMA, 2018). In order to use drugs in an ELDU manner, licensed veterinarians must possess an active veterinarian-client-patient relationship (VCPR) with the food animal operation (AVMA, 2018) and justify that any other approved drug would not be effective for treating the specific condition. The most common drugs proposed to treat pain and inflammation around calving are non-steroid anti-inflammatory drugs (NSAIDs). These NSAIDs are carprofen, flunixin meglumine, meloxicam and aspirin.

Carprofen is approved in the U.S. for the treatment of pain and inflammation associated with osteoarthritis in dogs, and can be used in dairy cattle in an ELDU fashion under AMDUCA regulations (Smith et al., 2008). However, its benefits in cow performance and health have not yet been proven. In a recent study (Meier et al., 2014), where dairy cows were treated with carprofen during the first and third week after parturition, no benefits were reported regarding milk yield, health and reproductive performance.

One of the most common NSAIDs used for the treatment of inflammation and pain in cattle is flunixin meglumine. Flunixin meglumine is approved by the FDA for both the treatment of fever associated with bovine respiratory diseases, and inflammation associated with endotoxemia in dairy cattle (FDA, 2018). Although flunixin meglumine can be used in cattle to treat pain in an ELDU manner, administering this drug by any route different from the one established on the drug label (strictly IV) is not allowed under AMDUCA conditions (Smith et al., 2008). Regardless, several studies have reported negative effects of flunixin meglumine treatment after parturition in cattle, such as an increased retention of fetal membranes, stillbirth, metritis, and decreased milk production (Waelchli et al., 1999; Newby et al., 2017).

The NSAID that has been increasingly used in cattle over the last several years is meloxicam. Similar to carprofen, meloxicam is approved for the treatment of pain associated with osteoarthritis in
dogs (Smith et al., 2008). Although meloxicam may have some promising features for pain treatment in cattle, in a large study where dairy cows were treated with a single dose of meloxicam or placebo 24 h after parturition, treatment affected neither the milk production nor the prevalence of diseases in treated animals (Newby et al., 2013).

Acetylsalicylic acid, better known as aspirin, is perhaps the most commonly used NSAIDs in general medicine worldwide (Vane and Botting, 2003). Unfortunately, aspirin products cannot be used in cattle under AMDUCA regulations because aspirin does not have a new animal drug application number, and therefore, does not meet the grandfather clause of the Animal Drug Amendments of 1968 (Smith et al., 2008). Subsequently, the use of aspirin products in dairy operations is controversial. Nevertheless, aspirin products are an attractive alternative for dairy producers to treat pain related to inflammatory conditions due to its easy administration, short milk and meat withhold, and low cost. The latest withdrawal time published by FARAD for aspirin was 24 h in both milk and meat (Smith et al., 2008).

Several studies have evaluated the effects of aspirin treatment after parturition on productive and reproductive performance, as well as the prevalence of diseases. A recent study, where sodium salicylate was administrated in drinking water to dairy cows for seven days following parturition, reported that treated cows had decreased NEFA and BHB concentrations in blood, leading to an exacerbated negative energy balance during the early postpartum period (Farney et al., 2013a). However, the same study reported that multiparous cows (3rd+ lactation) treated with aspirin had increased milk production and milk fat compared to untreated animals (Farney et al., 2013b). Supporting the latter study, Bertoni et al. (2004) reported that dairy cows that were treated with acetylsalicylic acid for 5 days after parturition had increased milk yields at the peak of lactation. More recently, Carpenter et al. (2016) treated dairy cows with sodium salicylate every 24 h for 3 days after calving, and reported that treated cows had increased daily and 305-d mature-equivalent milk yields compared to control cows.

In recent studies, organic dairy cows (n = 563) within the first 12 h after calving were treated with four oral administrations of aspirin or a placebo every 12 h (Barragan et al., 2017a, b). This treatment approach is shorter (2 days), ensures accurate individual drug dose, and may fit better within the logistics of large modern dairy operations compared to previous research (treatment performed at morning and afternoon health checks). Authors reported that cows treated with aspirin had decreased concentrations of SP 36 h after parturition, tended to have decreased concentrations of HP during the first week of lactation, produced more daily milk (2 kg/d) during the first 30 DIM and had lower SCC during the first five DHIA tests compared with cows treated with the placebo (Barragan et al., 2017a, b). The results from these
studies suggest that a short duration of anti-inflammatory therapy may decrease the inflammatory response in dairy cows early in the post-partum period, likely improving cow comfort and dry matter intake, thus decreasing the negative energy balance and enhancing milk production and udder health.

In conclusion, pain, inflammation and stress during the peri-parturient period can negatively affect the well-being and performance of dairy cows during the early lactation. Different alternatives have been proposed to treat pain and inflammation after calving in dairy cows. However, controversy still exists regarding the type of drug used, route of administration and length of treatment. Growing research is helping to elucidate the physiological processes involved during calving, and the effects of pain medication on improving welfare and performance of dairy cows in the early lactation period. Recent research showed promising results regarding the use of a short-term treatment with aspirin to treat pain and inflammation after calving. Although NSAID treatment after calving may decrease pain and inflammation, pain treatment should be utilized as a temporary strategy for improving welfare and performance in dairy cows after calving. Further efforts should be aimed at identifying preventive strategies (e.g., dry cow comfort, nutrition) for advancing cow comfort and diminishing the negative energy balance, stress and inflammation during and after calving, thus improving animal well-being and performance during the early lactation period.
References