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THE EFFECT OF MELOXICAM ON THE ABILITY OF NEONATAL DAIRY CALVES TO ABSORB IGG PROVIDED BY COLOSTRUM REPLACER

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by

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ABSTRACT

THE EFFECT OF MELOXICAM ON THE ABILITY OF NEONATAL DAIRY CALVES

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The objective of this study was to determine the effect of meloxicam, administered either in pill form immediately prior to colostrum replacer (**CR**), or powder form, mixed in solution with CR, on the immunoglobulin G (**IgG**) uptake, growth, and health of pre-weaned calves. A pilot study considering the potential benefits of meloxicam in pre-weaned heifers indicated administration of the drug following difficult parturition improved body weight (**BW**) and overall health, but was not associated with passive transfer of immunity (Murray et al., 2015). However, calves from this study were sampled from 10 commercial farms, and therefore, treatment administration was inconsistent, indicated by highly variable passive transfer rates from farm to farm.

A total of 30 Holstein dairy calves (16 bulls and 14 heifers) with an average BW of 44.3 kg were housed in a naturally ventilated enclosed calf room and blocked by expected birth date. Calves were removed from the dam within 30 min, prior to suckling, weighed, and randomly assigned to 1 of 3 treatments in a randomized complete block design. Treatments were as follows: (1) CR at 0 hours with no meloxicam (control, **CON**), (2) 1 mg/kg meloxicam in pill

form, before administration of CR (**P**), or (3) 1 mg/kg meloxicam during administration of CR, crushed and mixed into solution (**S**).

All calves were fed 675 g dry matter (**DM**) CR for a total fluid volume of just over 3 L, providing a dose of 180 g IgG. Beginning at 24 h of life, calves were offered 432 g DM of milk replacer (**MR**) (24% CP, 17% fat) daily, split into 2 feedings. Free choice textured starter and water were offered from 24 hours until completion of the study at 42 d. Blood samples were collected at 0 h to analyze initial serum IgG and circulating ketone concentrations, and at 6, 12, 18, and 24 h of life to analyze IgG uptake. Blood samples were collected weekly thereafter for analysis of glucose, plasma urea nitrogen (**PUN**), and blood ketone concentration. Measurements such as time of consumption for MR, BW, length, hip and withers height, and heart girth were also recorded weekly.

There was no effect of meloxicam on skeletal measurements or average daily gain (**ADG**); however, calves having received meloxicam in pill form before CR administration tended to gain length at a faster rate (cm/d) than those having received colostrum crushed into powder and mixed into solution. There was no significant effect of meloxicam on MR intake, time of consumption for MR, total DMI, or feed efficiency; however, calves having received meloxicam tended to consume a greater amount of starter than those having received the CON treatment. This coincided ketone levels which tended to be greater in blood samples from calves having received meloxicam, compared to those which did not, indicative of greater rumen development. There was no effect of meloxicam on PUN. Calves having received meloxicam in pill form had lesser blood glucose concentrations than those having received meloxicam in powder form, mixed into solution. While all calves met passive transfer, and meloxicam did not

affect apparent efficiency of absorption (**AEA**) of IgG, serum total protein (**STP**), or IgG uptake at 6, 18, and 24 h after birth, calves having received the drug did show decreased IgG uptake at 12 hours. Results of this study suggest that administration of meloxicam at 0 h offers positive effects on starter intake, and therefore rumen development of pre-weaned dairy calves. The dosing of meloxicam in pill form prior to CR, as compared to powder form in solution, also offers positive results for rumen development, indicated by lower blood glucose levels.

CHAPTER ONE

REVIEW OF LITERATURE

INTRODUCTION

Efficiency of food production is more urgent than ever, as global populations, and

therefore demand for nutritious foods, are rapidly increasing (United Nations Department of

Economic and Social Affairs, 2015), while greenhouse gas emissions are simultaneously

expediting the effects of global warming (Intergovernmental Panel on Climate Change, 2014).

Dairy is a global industry which will remain invaluable in meeting these challenges of food

security, currently feeding over 7 billion people, and providing work for more than 1 billion

(International Farm Comparison Network, 2018).

As developing countries advance, global population is expected to increase from 6.8

billion to 9.1 billion by the year 2050, while simultaneously becoming wealthier (Food and

Agriculture Organization of the United Nations, 2009). As observed over the last 50 years,

increased wealth results in greater purchasing power, and therefore, greater consumption. The

rise in both number of people, as well as financial status, has and will continue to prompt a larger

demand for food sources, such as animal proteins (Godfray et al., 2010). Fortunately, while both

population and demand have increased over the last half-century, food production has also

accelerated, allowing for a significant reduction in the proportion of the world's people who are

hungry (Food and Agriculture Organization of the United Nations, 2009).

In order to continue to strive to meet this growing demand, the agricultural industry must

find more efficient ways to utilize its resources in the production of food. By improving

production of dairy animals in particular, dairy operations are able to become more profitable,

and are therefore more likely to remain in business, which stabilizes the supply of these foods. In addition to more successfully meeting increased global demands for food, improved herd efficiency reduces environmental impacts of farming. This is because an efficient animal will emit fewer greenhouse gasses, producing less methane and nitrous oxide per unit of product, as compared to an average animal (Waghorn et al., 2011). This is especially important currently, as global warming trends are continuing to advance at a rate that is unparalleled (Intergovernmental Panel on Climate Change, 2014).

In order to improve efficiency of the dairy industry, farmers must implement well-rounded practices, which encourage health and productivity of more than just the lactating herd. This is because the productivity of the lactating herd is contingent upon many other considerations, with calf and heifer health among the most important. Short term benefits of optimizing calf and heifer health include improved intakes, and gains, while long term effects include greater milk yields and components in first and second lactations, compared to less healthy youngstock. The effects of management practices which optimize calf health, such as maximization of immunoglobulin uptake from the timely feeding of good quality colostrum on day one of life, have been observed to carry over to the productivity and efficiency of the animal even once it reaches maturity. Meloxicam is a non-steroidal anti-inflammatory drug (**NSAID**) with the potential for reducing inflammation following the birthing period, and improving the uptake of immunoglobulins; thereby improving the health of the calf, and the overall efficiency of the milking herd once these animals enter lactation.

HEALTH OF THE PRE-RUMINANT CALF

To run a successful dairy requires best management practices, with attention to details beyond those associated with the lactating herd. The health of the milking herd depends on the

consideration given to many other factors, especially calf and heifer rearing. This is because healthy calves are more likely to be productive, both during and after maturation (Robison et al., 1988; DeNise et al., 1989). For example, one study found that the incidence of diarrhea, septicemia, and respiratory disease significantly decreased calf height and weight in the first 6 months of life (Donovan et al., 1998). Moreover, the number of days that calves were treated for pneumonia during the first 6 months significantly decreased the average daily gain (**ADG**) during the following 6 months (Donovan et al., 1998). Calves that have improved health, and therefore growth, are likely to consume more feed. This was observed in a study which considered data from 335 calves raised over 3 years, and reported that calves with weight gains below the mean ADG of the group had reduced starter intake (Kertz et al., 1984).

Growth and starter intake are important benchmarks to consider when raising healthy and productive calves, as solid feed intake during both the pre and post-weaning period are highly correlated with ruminal development (Tamate et al., 1962). A study which differentiated amongst calves fed only milk and those fed a traditional diet of milk, hay and starter, found greater development of the papillae and musculature within the reticulo-rumen of calves offered solid feed (Tamate et al., 1962). The limited development of rumen epithelium, size, and musculature in calves fed only milk is most likely caused by the automatic closure of the esophageal groove when calves voluntarily consume milk, which causes the milk to bypass the rumen and instead be directly shunted to the abomasum (Baldwin et al., 2004). Solid feed, however, will not bypass the rumen, and therefore contributes to rumen development, which in turn, promotes greater starter intake and body weight (**BW**) gain following the weaning period (Khan et al., 2011).

The rumen of a newborn calf is non-functional, and the animal is therefore considered a pre-ruminant. The rumen develops over time as an animal matures and begins consuming more solid feed, resulting in the establishment of anaerobic microbiota in the gut (Baldwin et al., 2004; Khan et al., 2011). The coupling of these factors, both the inhabitation of microorganisms in the gut and increased solid feed intake, initiates the fermentation of fiber and other carbohydrates present in solid feeds, and the absorption of the fermentation products, known as volatile fatty acids (**VFA**) (Quigley et al., 1991).

As this process takes place, and ruminal microbes break down and utilize nutrients from carbohydrates in the feed, less carbohydrate becomes available for digestion after the rumen. For this reason, the amount of glucose available to the animal from the diet declines, and the energy supply of the animal shifts from glucose, previously supplied by milk, to volatile fatty acid byproducts of fermentation (Baldwin et al., 2004). As a result, the metabolic activity of the liver shifts from glycolytic to gluconeogenic, utilizing the VFA, propionate, as a precursor (Baldwin et al., 2004). During this transitional period of development from pre-ruminant to ruminant, blood parameters for glucose will decrease over time, while beta-hydroxy butyrate (**BHB**), a ketone produced for energy, via the metabolism of the VFA, butyrate, will increase (Baldwin et al., 1992). It is also expected that circulating plasma urea nitrogen (**PUN**) levels will increase with time (Chapman et al., 2017), as bacteria actively catabolize amino acids present in solid feed, producing ammonia, which will be detoxified in the liver when converted to urea (Berends et al., 2014).

Volatile fatty acids are well understood to be instrumental in development of the rumen epithelium. For example, the supplemental feeding (Gilliland et al., 1962; Rice, 2017) or infusion (Tamate et al., 1962) of VFA salts to calves both pre and post-weaning has been observed to

significantly improve development of ruminal mucosa. As the microbes within the rumen of the

calf begin to ferment more solid feed, specifically starter, the resulting VFA byproducts will

contribute to the maturation of the rumen. Not only is there a marked development of the ruminal

papillae, but also an increase in ruminal mass and musculature, which improves the calf's ability

to absorb nutrients from the breakdown of feed (Figure 1) (Jones et al., 2017). This allows the

animal to grow more efficiently, maturing at a faster rate, to therefore become more productive.

Figure 1. Comparison of 6-week ruminal development of calves fed (A) only milk, (B) milk and
starter, or (C) milk and hay (Pennsylvania State University Extension, 2017)
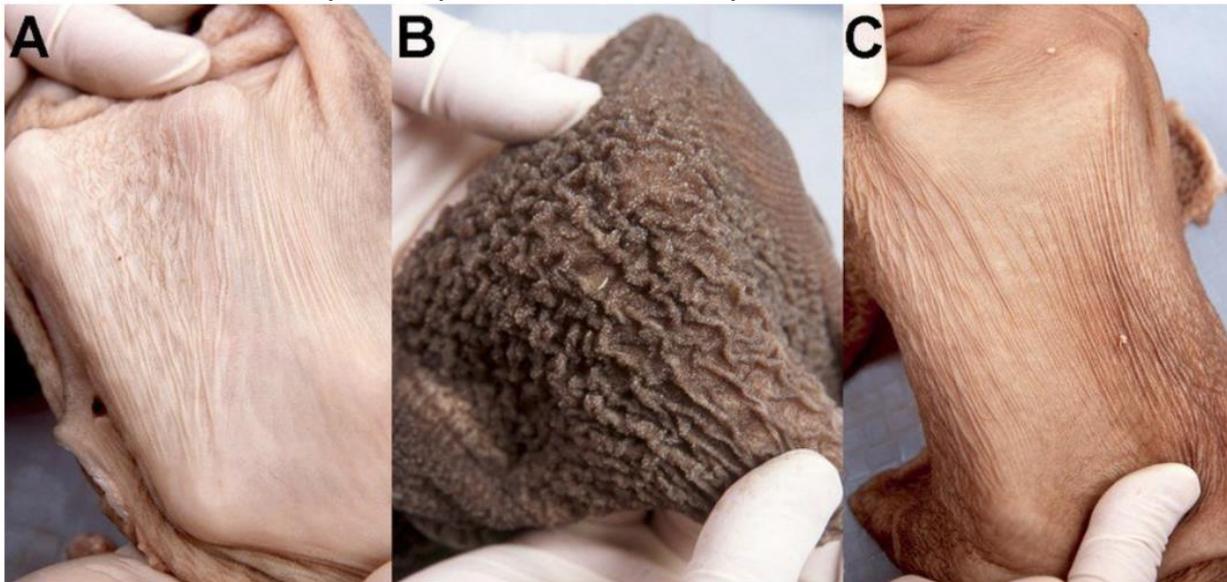
As a result of this improved utilization of feeds, it is more likely that heifers reach a pre-

breeding target weight in order to be bred in a timely and cost-effective manner, optimizing

reproductive performance (Patterson et al., 1992). Moreover, a correlation between ruminal

development and milk production has also been reported. For example, a meta-analysis of effects

of pre-weaned calf nutrition on first-lactation performance, considering 9 studies and 21

treatment groups found a positive relationship between pre-weaning starter dry matter intake and

first lactation performance (Gelsinger et al., 2016). Pre-weaned calves that consumed at least 100

g of starter dry matter (**DM**) per day in addition to their liquid diet, were expected to produce 127 kg more milk, 8.4 kg more fat, and 4 kg more protein as compared to pre-weaned calves that did not consume starter. These results are congruous with those reported by Rauba et al. (2019), which revealed a positive relationship between starter protein and metabolizable energy intake in the first 6-8 weeks of life with first lactation milk, fat, and protein production. Both of these studies indicate that calves with greater starter intake, and therefore improved ruminal development, which are able to utilize nutrients from feeds more efficiently, are more productive when entering into lactation.

The productivity of the herd depends on health and success of the calf. Optimizing calf health involves employment of best management practices beginning on the first day of life; the effects of which have been observed to carry over to the productivity of the animal even after it has reached maturity, or entered lactation (DeNise et al., 1989; Faber et al., 2005). Arguably most imperative of these practices is the timely and adequate feeding of quality colostrum, and maximizing its uptake in the neonatal calf (Godden, 2008).

THE IMPORTANCE OF FEEDING COLOSTRUM

Colostrum is the first mammary secretion produced by the dam during the initial day after calving (Pakkanen, 1997). It contains serum proteins and other components of lacteal secretions which are accumulated in the mammary gland beginning several weeks before calving (Foley et al., 1978). Distinguishable from transition milk and whole milk, it is densely packed with nutrients, such as proteins, fats, carbohydrates, vitamins, minerals and water (Foley et al., 1978), as well as immunologically active maternal cells and other components, like immunoglobulins (**Ig**), leukocytes, macrophages, lymphocytes, and neutrophils (Larson et al., 1980). Total solid content of colostrum is reported to average 23.9% percent, decreasing with each successive

milking, as compared to whole milk, which averages 12.9% solids. Much of this increase is attributable to a more than 4-time increase in protein content, particularly Ig and casein. Additionally, the fat content of colostrum averages 6.7%, which is nearly double that of milk, at 3.6%. Many vitamins and minerals have also been detected in increased concentrations (Foley et al., 1978). All of these components are necessary for calf vitality, and have many functions which are crucial for calf health. High concentrations of fat and lactose are essential for thermoregulation and energy balance (Murray et al., 2013; Kirovski, 2015), water is key for maintenance of hydration, and arguably most important, immunologically active cells and proteins are imperative for passive immunity (Godden et al., 2008).

Passive immunity is the short-term ability of the calf to resist infection, achieved by the action of antibodies (Brambell, 1958), or Ig, which are introduced from the colostrum of the dam (McGuirk, 2004) or colostrum replacer (**CR**) (Swan et al., 2007). Because cattle have a synepitheliochorial placenta, which prevents the transfer of Ig from the dam to the fetus, calves are born hypogammaglobulinemic (Lopez et al., 1988), and can only achieve transfer of passive immunity via the adequate and timely feeding of quality colostrum (Arthington et al., 2000) or CR. The success of transfer of passive immunity depends on the absorption of Ig across the small intestine within the first 24 h following birth (Quigley et al., 1998). This allows the calf protection from pathogenic organisms until its own immune system matures around 4 to 5 weeks of life (Gelsinger et al., 2017).

While consumption of good quality colostrum or CR early after calving is immediately beneficial for reducing morbidity and mortality rates (Figure 2) in pre-weaned calves, long-term effects have also been observed (Robison et al., 1988; DeNise et al., 1989; Faber et al., 2005). These include reduced post-weaned mortality rates, improved rate of gain and feed efficiency,

reduced age at first calving, as well as cull rates in the first lactation, and improved milk yield in the first and second lactations.

Figure 2. Calf survival by serum IgG concentration up to 8 weeks of age (USDA, 1993)
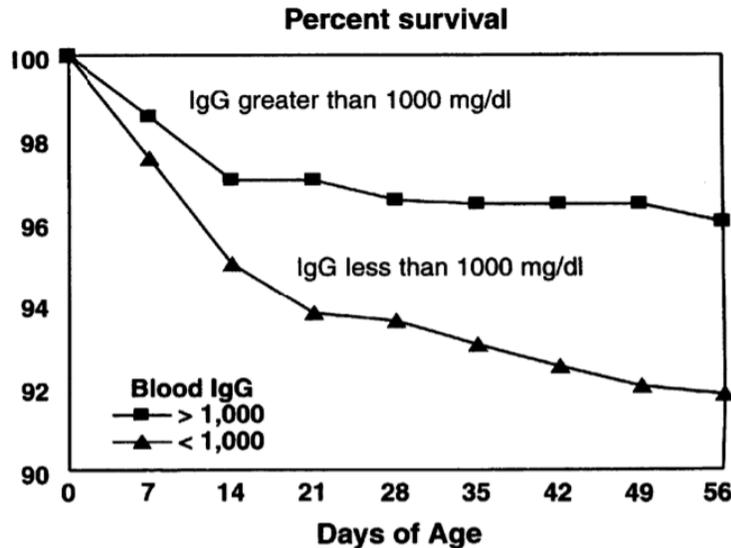
COLOSTROGENESIS AND IMMUNOGLOBULINS

Colostrogenesis, or the production of colostrum, requires the pre-partum transfer of circulating Ig to the mammary gland (Foley et al., 1978). This process begins several weeks before parturition, and abruptly terminates immediately prior to birth (Brandon et al., 1971), peaking 1-3 days before parturition (Weaver et al., 2000). It is regulated by the lactogenic hormones, estrogen, progesterone (Smith et al., 1971; Barrington et al., 2001), and prolactin (Barrington et al., 1997), and allows for the transfer of up to 500 g Ig per week from maternal circulation into mammary secretions (Brandon et al., 1971).

Immunoglobulins are proteins in the blood which function to respond to and counteract specific toxins or foreign bodies (Casali et al., 1996). As previously outlined, because the transfer of Ig from the dam to the bovine fetus does not occur in utero, the immune response of the neonatal calf is immature, and they must instead consume colostrum as soon as possible

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(McGuirk, 2004), and no later than 24 h following parturition (Chester-Jones et al., 2009). The 3 major classes of Ig transferred from maternal serum to colostrum during colostrogenesis are immunoglobulin G (**IgG**), immunoglobulin M (**IgM**), and immunoglobulin A (**IgA**) (Butler, 1969).

Immunoglobulin G, particularly IgG_1, represents most of the total Ig present in both colostrum, and the serum of the dam (Table 1), as well as that of the calf. While much is still left to be understood about the mechanisms of colostrogenesis, it is believed that there is a specificity for the transfer of IgG_1 from the serum into the mammary gland of the dam (Butler, 1969), facilitated by receptors on the mammary alveolar epithelial cells (Barrington et al., 1997, Larson et al., 1980). This is evidenced by the fact that although IgG_1 and IgG_2 exist in about equal parts in maternal serum, IgG_1 is much more prevalent in colostrum, constituting about 90% of the total IgG, and existing in amounts much greater than IgG_2 (Table 1) (Barrington et al., 2001).

Table 1. Immunoglobulin G concentrations (mg/mL) in bovine serum, colostrum, and milk (Barrington et al., 2001)

Immunoglobulin	Serum	Colostrum	Milk
IgG-total (mg/ml)	25.0	32–212	0.72
IgG1	14.0	20–200	0.6
IgG2	11.0	12.0	0.12

Transfer of IgG_1 from maternal serum to colostrum is initiated by an increase in estrogen and a decrease in progesterone (Smith et al., 1971; Barrington et al., 2000). The role of estrogen and progesterone levels in the transfer of IgG during colostrogenesis has been observed in numerous studies. For example, research conducted using injections of estrogen and

progesterone to artificially induce lactation showed that before lactation began, concentrations of IgG_1 in mammary secretions increased to eventually mirror that of colostrum (Smith et al., 1973; Winger et al., 1995). These results suggest that estrogen and progesterone have influence on the receptor responsible for selective transport of IgG_1. At the onset of lactation, expression of this receptor ceases, likely in response to rising levels of the lactogenic hormones, prolactin (Barrington, 1997) and glucocorticoids, surrounding this transition period (Brandon et al., 1975; Barrington et al., 2001). As a result, IgG is no longer transferred across the mammary epithelium into the lumen.

Transfer of IgG_1 is also regulated locally. This has been supported by research which applied experimental treatments to individual udder halves (Brandon et al., 1975; Guy et al., 1994). For example, one study, which applied continuous milking to one udder-half and allowed a normal dry period for the other udder half, reported a tendency for reduced transfer of IgG_1 in secretions from udder halves in which milking was maintained. Oppositely, colostrogenesis appeared normal in the mammary glands of the opposite udder halves, which were not milked through the dry period (Brandon et al., 1975). The differences in Ig transfer of each of the udder halves demonstrates the ability for local signals to dominate systemic signals, regardless of hormonal influence associated with late gestation (Brandon et al, 1975).

Immunoglobulin M makes up less than 10% of the serum and colostral Ig (Klaus et al., 1969), and is understood to have significant involvement in the primary immune response (Rose et al., 1964; Butler, 1969). Additionally, this Ig is reported to have an integral part in the process of agglutination (Rose et al., 1964). Agglutination is the clumping of bacterial cells through the binding of antigenic components on the surface of the cells to the antibody (Stavitsky, 1998). IgM has also been observed to have an important role as a complement-fixing antibody (Rose et

al., 1964; Butler, 1969). Both of these processes, agglutination and complement-fixing, result in the formation of an antibody-antigen complex, also known as an immune complex (Nydegger, 1998), which elicits an immune response.

Opposite of humans and most other species (Porter et al., 1970; Ulfman et al., 2018), IgA exists in very minor concentrations of calf serum, as well as bovine maternal colostrum (**MC**) (Butler et al., 1972). Immunoglobulin A is thought to be synthesized locally in the mammary gland, as it is in other species (Asofsky et. al, 1968). Due to its limited concentration in bovine colostrum and milk, not very much research exists pertaining to its exact biological function in ruminants. However, because IgA is the main isotype of all the immunoglobulins found in milk and colostrum of humans, as well as other species, (Porter et al., 1970; Ulfman et al., 2018), its applications are well-defined. In non-ruminant species, IgA is understood to neutralize and kill pathogens, and to regulate the neonatal immune system, providing protection against the inflammatory response (Ulfman et al., 2018). One study compared the activity of purified colostral immunoglobulin preparations of IgG, IgA, or IgM to that of normal colostrum, in calves challenged orally with *Escherichia coli*. This study reported that while all individual preparations were less effective than colostrum, IgA was least effective compared to IgG and IgM. Calves having received purified IgA experienced prolonged diarrhea, in addition to other symptoms (Logan, 1974). The results of this study indicate the limited role of IgA in the immunity of the calf compared to the other Ig present in colostrum, especially IgG.

FAILURE OF TRANSFER OF PASSIVE IMMUNITY

Risks associated with failure of transfer of passive immunity (**FTPI**), defined as fewer than 10 g/L of circulating plasma IgG concentration (McGuirk, 2004) at approximately 24 h of life, include increased morbidity and mortality rates, both pre and post-weaning, as well as long-

term decreases in productivity (Robison et al., 1988; DeNise et al., 1989). A study which compared IgG_1 concentrations of calves less than 3 weeks of age that died of infectious diseases with that of calves that presented as clinically normal, found that dead calves had significantly lower circulating IgG. Specifically, 50% of those calves had serum IgG values more than 2 standard deviations from the mean of the experimental group, while 35% had serum IgG values more than 1 standard deviation from the mean (McGuire, 1976). The results of this study highlight the implications of FTPI on calf mortality rates.

In order to test calves for FPTI either serum IgG concentrations (Pfeiffer et al., 1977) or serum total protein (**STP**) concentrations (McBeath et al., 1971) can be measured. There are a number of methods which have been developed for measuring serum proteins and success of transfer of passive immunity. Although each have their own limitations, some of those most popular are the measurement of serum IgG concentrations via radial immunodiffusion (**RID**) (Pfeiffer et al., 1977), or measurement of serum total solids on farm via refractometer (McBeath et al., 1971). Measurement of serum proteins in calves is beneficial for determination of the success of a farm's colostrum management program. Currently, 35.3% of heifers are raised on farms which routinely monitor STP, the majority of which are likely from large operations (USDA, 2014). This is because while 38.3% of large farms routinely monitor STP, less than 6.2% of all operations do so (USDA, 2014).

Calves with serum IgG levels measured as less than 10 g/L (McGuirk, 2004) or serum total protein levels less than 5 g/dL (Weaver, 2000) to 5.5 g/dL (Tyler et al., 1996) at 24 h of life can be treated with 20 mL/ kg intravenous (**IV**) plasma, or whole blood at an increased dose (Weaver et al., 2000). The decision to treat a calf for FTPI with transfusion depends on the value of the calf, the calf housing environment, and the ability to administer IV plasma or blood.

Although calves suffering from FTPI are at an increased risk of disease development, transfusion is not always necessary, as they can survive if they are placed in a warm, clean, and dry environment, with low exposure to pathogenic organisms, until their own immune systems have the chance to develop (Weaver et al., 2000).

Likewise, IgG and STP levels greater than 10 g/L and 5.5 g/dL, respectively, do not guarantee calf survival. This was evidenced in the 5% baseline mortality rate observed even in animals with the highest transfer of passive immunity (Weaver et al., 2000). Baseline mortality rates are influenced by management strategies surrounding exposure of calves to pathogens, calf hygiene, and nutrition. As previously outlined, when serum Ig concentrations decrease, risk of mortality and morbidity increase, but this risk is relative to the baseline mortality rates on each individual farm. For this reason, it should not be expected that calves raised on farms with poor hygiene, inadequate nutrition and increased exposure to pathogens will maintain good health and productivity if transfer of passive immunity is achieved (Weaver, 2000). This is based on observations made from a study conducted over a 10-year period at a calf-rearing operation which sampled 3,479 calves received from 25 farms. Such observations included a lack of significant interaction between baseline mortality and STP concentrations, in addition to a lack of a significant decrease in mortality rates in calves with adequate to high transfer of passive immunity (Tyler et al., 1998).

While the progress has been made over the last 30 years (Figure 3), the estimated prevalence of FTPI in the United States is still 19.2% (Beam et. al, 2009). During 2010, 4.2% of pre-weaned dairy heifers died, the majority of which having suffered from pneumonia, or inflammation of the tissues of the lungs, commonly caused by bacterial or viral infection (USDA, 2012). In addition to the immediate monetary consequences associated with increased

prevalence of death and disease amongst young cattle, hypogammaglobulinemic calves have also been associated with lower ADG, as well as decreased milk yield and increased culling rates during the period of first lactation (DeNise et al., 1989; Faber et al., 2005). An analysis of costs associated with calf morbidity, mortality, and production losses does not yet exist for the United States; However, a European meta-analysis estimated that the total cost per calf with FTPI was about 60 euros, or just greater than $71 (Raboisson et al., 2016). Furthermore, high mortality rates alone associated with the significant number of calves that suffer from FTPI costs the industry hundreds of millions of dollars per year (Pritchett et al., 1991).

Figure 3. Percentage of heifer calves with failure of transfer of passive immunity by herd size (USDA, 2010)
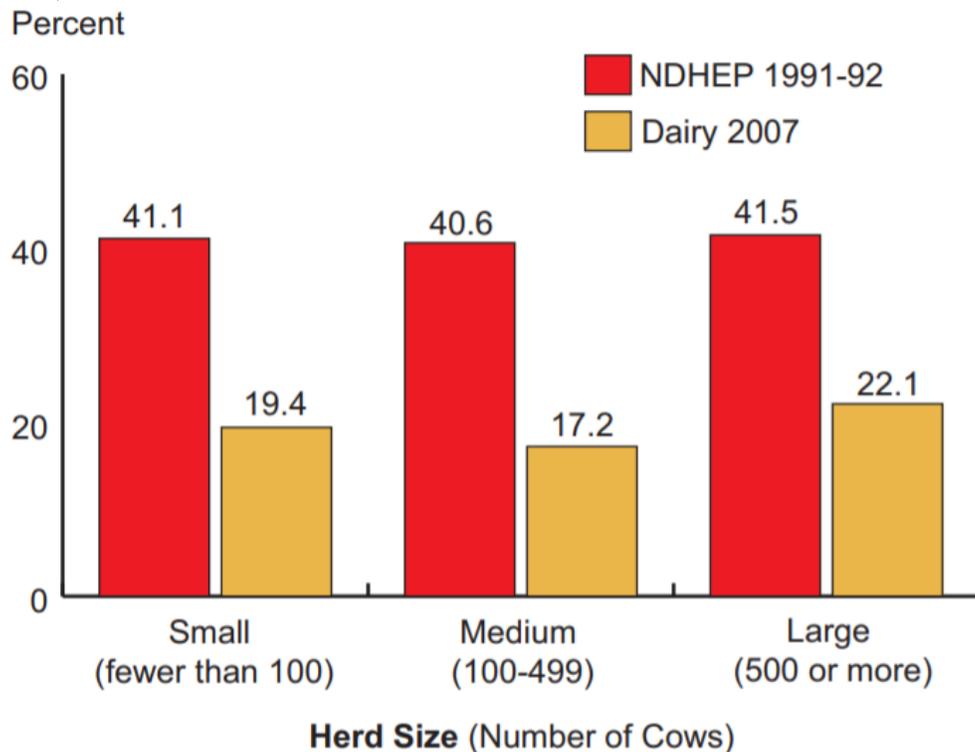
*NDHEP (1991-1992)- Transfer of passive immunity status measured by the National Animal Health Monitoring System (**NAHMS**) during the National Dairy Heifer Evaluation Project
*Dairy 2007- Transfer of passive immunity status measured by NAHMS during the Dairy 2007 Study

FACTORS EFFECTING FAILURE OF TRANSFER OF PASSIVE IMMUNITY

AND APPARENT EFFICIENCY OF ABSORPTION

In comparison to that of a mature animal, the cells lining the small intestine of the neonatal calf have the unique ability to non-selectively absorb Ig as whole macromolecules, most successfully during the first 24 h of life (Michanek et al., 1989). Once these antibodies are absorbed across the intestinal lining, they gain access to the circulatory system through the lymphatic system via the thoracic duct (Staley et al., 1972). Between 24 and 36 h, the absorption of Ig and other large macromolecules through the enterocytes terminates (Weaver, 2000). It has been observed that feeding colostrum shortly following birth results in earlier interruption of intestinal permeability to Ig, at an average of 24 h post-partum, while delayed feeding results in delayed gut closure, until enterocytes spontaneously cease to absorb Ig into circulation (Stott et al., 1979). The mechanisms behind this process, known as gut closure, are not yet well understood.

Though not all, many of the factors which effect the apparent efficiency of absorption (**AEA**) of Ig in the calf, and the success of transfer of passive immunity can be controlled with best management practices. The most important considerations are the quality and source of the colostrum consumed, the time to the first feeding, and the method of administration (Weaver et al., 2000).

Colostrum Quality

The quality of MC, or the concentration of Ig available to the calf, produced by the dam, has significant impacts on the ability of the calf to achieve adequate transfer of passive immunity (Weaver et al., 2000). Some factors which influence MC quality include breed and age or parity of the dam (Weaver et al., 2000), nutrition surrounding colostrogenesis (Aragona et al., 2016),

volume of colostrum produced (Weaver et al., 2000), length of the dry period (Brandon et al., 1975), and health of the mammary gland (Maunsell et al., 1998).

It is recommended that 4 L of high-quality colostrum or CR, with a concentration of at least 50 g IgG, be fed as soon as possible after birth (Morin et al., 1997). This recommendation is based on observations of health and productivity of the calf both before and after the weaning period. While only 13% of producers routinely evaluate MC, and 56% of which do so only by employing methods such as visual inspection (USDA, 2007), colostrum quality can and should be determined. Most accurate analysis is completed in a lab by radial immunodiffusion, but can also be determined on farm, with either the use of a colostrometer (Fleenor et al., 1980), or Brix refractometer (Quigley et al., 2013, Chigerwe et al., 2008).

Compared to values obtained by RID, measurement of specific gravity via colostrometer has been reported to have an average correlation coefficient of 0.77 (Bartier et al., 2015), ranging from 0.63 (Quigley et al., 1994) to 0.87 (Mechor et al., 1992). In a study estimating the efficacy of using specific gravity to predict gamma-globulin concentration, it was reported that total solids and specific gravity are related ($P<0.01$), and because 64% of total solids consist of protein, specific gravity and total protein are also related ($P<0.01$). Further, because 47% of total protein is constituted of gamma-globulins, a relationship exists for specific gravity and gamma-globulins IgG, IgM, and IgA ($P<0.01$) (Fleenor et al., 1980).

When using a colostrometer, colostrum with a specific gravity of ≤ 1.035 is considered poor quality, with an estimated Ig concentration of ≤ 21.8 mg/mL. Colostrum with a specific gravity ranging from 1.036 to 1.046 is considered to be of moderate quality, with an estimated Ig concentration of 24.35 to 49.82 mg/mL, respectively. Finally, the specific gravity of excellent quality colostrum ranges from 1.047 to 1.076, and has a predicted Ig concentration of 52.36 to

126.62, respectively (Fleenor et al., 1980). It should also be noted that temperature has been reported to affect the predicted value of colostrum Ig concentration ($P<0.01$) when using a colostrometer. For this reason, a conversion chart should be used to determine Ig concentration, depending on the temperature of the colostrum (Mechor et al., 1992).

Brix refractometers consider the refractive index of colostrum, which is significantly correlated to total solids, and therefore Ig concentration. Measurement of total solids determined via Brix refractometer has been reported to have a correlation coefficient to RID ranging from 0.64 (Chigerwe et al., 2008; Bartier et al., 2015) to 0.75 (Quigley et al., 2013). In a recent study, it was reported that the cut point for estimation of high- or low-quality colostrum is about 21%. Colostrum with a Brix percentage more than 21% is considered good quality, approximated to have a concentration of $\geq$50 g IgG/L, while a Brix percentage less than 21% is considered poor quality, and predicted to have a concentration of $\leq$50 g IgG/L (Quigley et al., 2013).

While the colostrometer and refractometer are not a recommended tool for precise analytics, they are both useful, affordable methods for on farm prediction of the relative quality of colostrum. Either should be utilized in order to maximize absorption of vital Ig in the neonate (Fleenor et al., 1980). When MC of adequate quality is not available, replacement of colostrum may be implemented to provide appropriate immunity to the calf (Godden, 2008).

Source of Colostrum

Benefits of using CR in place of MC include easy storage, reduced risk of disease transmission (Pennsylvania State University Extension, 2016) or bacterial contamination (Pithua et al., 2009), and known values of IgG concentration without having to test for quality. While use of a CR is valuable under certain circumstances, such as feeding calves from dams on their first or second lactations (Tyler et al., 1999), or calves from dams with transmittable diseases (Pithua

et al., 2009; Pennsylvania State University Extension, 2016), it should be noted that greater STP values have been reported ($P<0.001$) in calves fed MC (6.1 ± 0.11 g/dL) compared to those fed 2 different types of CR (5.3 ± 0.11 g/dL) (Priestly, 2013). Similarly, serum IgG concentrations were greater ($P<0.0001$) for calves fed MC (2098 ± 108 g/dL) compared to calves fed a plasma-derived colostrum replacer (**PDCR**) (927 ± 107 g/dL) or a colostrum-derived colostrum replacer (**CDCR**) (1139 ± 108 g/dL). This study also reported that the proportion of calves having achieved transfer of passive immunity was greatest for those having received MC (91.8%) compared to those having received CDCR (49%) and PDCR (28.6%). Calves fed MC were observed to have greater weaning weights (61.2 ± 0.9 kg) ($P=0.01$) compared with calves fed CR (59.5 ± 0.9 kg), and greater gains in BW ($P=0.009$) compared to calves fed CR (Priestly, 2013).

Several studies have not only reported differences in the efficacy of MC compared to CR, but also the efficacy of lacteal based sources of CR compared to CR containing plasma derived protein (Priestly et al., 2013, Place et al., 2010). Upon statistical analysis of the study outlined above, it was discovered that calves fed MC weighed less at birth (35.9 ± 0.8 kg) ($P=0.02$) compared to calves fed CDCR (38.4 ± 0.8 kg), while no differences were found in initial BW between calves fed MC and calves having received PDCR (37 ± 0.8 kg). However, even though calves having received MC had the lowest birth weights, which were not statistically different from calves having received PDCR, weaning weights for calves having consumed MC (61.2 ± 0.9 kg) were greater than calves that consumed PDCR (57.2 ± 0.9 kg) ($P=0.002$), and similar to calves having received CDCR (59.5 ± 0.9 kg). Similarly, gains in BW were greater ($P=0.002$) for calves fed MC (24.6 ± 0.9 kg) than those which received PDCR (20.7 ± 0.9 kg) and similar to those fed CDCR (22.9 ± 0.9 kg). In comparing the different types of CR, it was found that weaning weights tended to be greater ($P=0.08$), and gains in BW tended to be increased ($P=0.09$) for

calves that received CDCR compared to those having consumed PDCR. Finally, calves in this study which were fed CDCR also had improved AEA (38.8$\pm$3%) ($P<0.001$) compared to calves fed PDCR (21.6$\pm$3%) (Priestly, 2013).

These findings are consistent with another study which compared only lacteal derived CR (**LDCR**) with PDCR, and found that AEA of calves fed LDCR (38.2$\pm$3%) was greater than that of calves fed PDCR (28.4$\pm$5%). Calves from this study fed LDCR also had significantly higher serum IgG concentrations at 24 h (14.7$\pm$2.9 mg/mL) than those fed PDCR (9.6$\pm$1.8 mg/mL), and made up a greater proportion (94.4%) of animals which reached adequate transfer of passive immunity compared to those fed PDCR (36.8%) (Place et al., 2010). Collectively, the results of these studies suggest that while a good quality MC is the best source of neonatal nutrition, CR derived from a lacteal source, such as colostrum, is more beneficial for the health and productivity of the calf compared to CR derived from plasma.

Other studies have considered the value of employing a colostrum supplement (**CS**) to enhance Ig absorption in the newborn calf (Morin et al., 1997). One study, which utilized 4 L of poor-quality colostrum (25.7 mg IgG/mL), supplemented calves with either 0, 136, or 272 g of IgG per meal via a colostrum derived CS. Researchers on this study speculated that substances within the supplement, or the drying process by which the supplement was made, may have interfered with IgG absorption, or enhanced the rate of gut closure, as serum IgG of supplemented calves was not significantly higher than those fed the poor quality colostrum. Moreover, AEA was lower ($P=0.009$) for calves supplemented with 272 g IgG per meal (18.13$\pm$2.48%) than that of calves fed the poor-quality colostrum (32.76$\pm$2.38%). Calves that were supplemented 136 g IgG per meal had an AEA (24.87$\pm$3.64%) which tended to be lower than calves that were not supplemented (Morin et al., 1997). The results of this study are

consistent with the findings of other investigators who also observed that supplementation of good quality colostrum, with products derived from colostrum or whey protein concentrate (Abel et al., 1993; Zaremba et al., 1993) had no effect on mean peak serum concentrations. The conclusions of these studies indicate that when good-quality MC is not available, colostrum supplementation may not be very beneficial to the health status of the calf. For this reason, CR should be utilized instead.

Time to First Feeding

Aside from the quality and source of colostrum offered, time to first feeding is one other important consideration. Farmers should aim to feed all calves as soon as possible after birth, and should even strive to feed calves before 6 h (Godden, 2008). A study considering 422 calves on 119 Canadian dairy farms observed that an increased volume of colostrum fed within 6 h of parturition significantly decreased risk of FTPI (Trotz-Williams, 2008). This is because absorption of Ig from colostrum is most optimal in the first 4 h post-partum, begins to decline after 6 h, and declines rapidly after 12 h (Godden, 2008). This is well understood, as calves fed similar volumes and qualities of colostrum after a shorter period of time following parturition have commonly been observed to have significantly elevated serum Ig concentrations, as compared to those fed later. Another study which fed pooled colostrum at 6, 12, 24, 36, or 48 h found that concentrations of IgG in the blood plasma of the calf as a percentage of the amount fed was 65.8% if fed at 6 h, 46.9% if fed at 12 h, 11.5% if fed at 24 h, 6.7% if fed at 36 h, and 6% if fed at 48 h. It was also reported that fecal IgG increased linearly with age (Matte et al., 1982). The negative relationship between serum IgG levels and age at first colostrum feeding observed (Figure 4) in these studies support a recommendation for feeding colostrum as soon as possible following birth.

Figure 4. Relationship between total plasma IgG and age at first colostrum feeding, 6 h after feeding (Matte et al., 1982)

$$Y = 9.469 - .374\,X + .0045\,X^2$$

Total Plasma IgG (Vg)

Age at time of colostrum feeding (h)
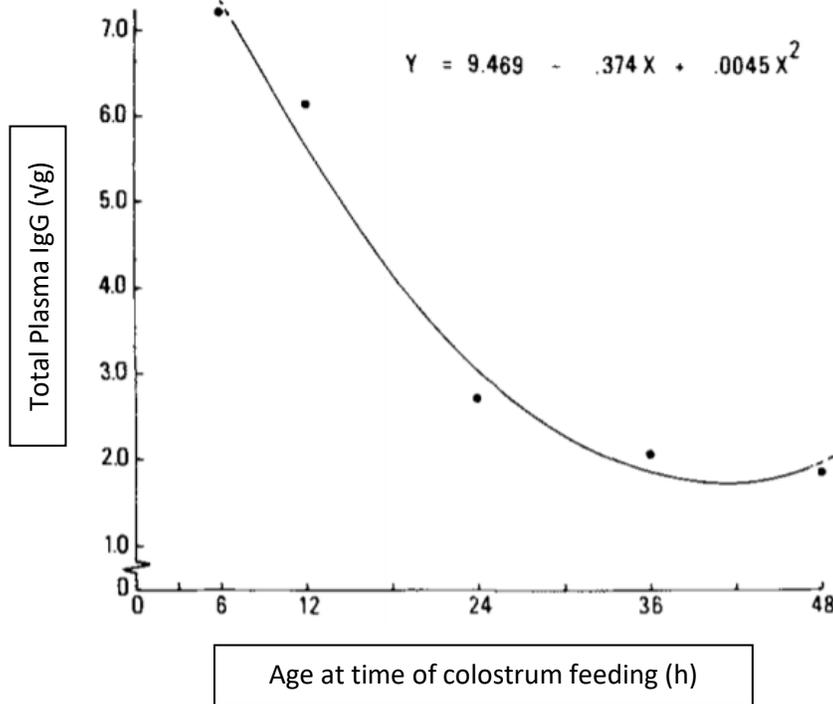
Method of Feeding

Attention should also be given to method of feeding (Besser et al., 1991; Weaver et al., 2000). Calves allowed to suckle from the dam will consume an unknown volume and quality of colostrum (Weaver et al., 2000), with some calves unwilling to voluntarily consume a sufficient volume in a timely manner. One study which distinguished between FTPI rates among different methods of feeding observed 61% FTPI in those allowed to suckle, 19% FTPI in those fed via nipple bottle, and 10% FTPI in those fed via esophageal tube (Besser et al., 1991). Calves allowed to suckle from the dam are also at risk of increased exposure to bacteria and other pathogens present in the raw lacteal secretions of the dam. This is because bacteria may bind free Ig in the gut (Johnson et al., 2007), or non-specific receptors on the neonatal enterocyte (Staley et al., 1985), interfering with uptake of macromolecules across the enterocyte. A study which fed the same volume and quality of colostrum, either pasteurized or raw, reported that calves fed

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pasteurized colostrum, containing 813 cfu/mL of bacteria, had significantly higher serum IgG levels as compared to the calves fed raw colostrum, containing 40,738 cfu/ mL of bacteria (Johnson et al., 2007). For this reason, it is recommended that calves be removed from the dam shortly after birth, and hand fed a known volume of good quality colostrum from a nipple bottle or via esophageal tube feeder. Finally, metabolic disturbances and stress related to the length, difficulty, and environment of parturition have also been understood to disturb Ig uptake.

EFFECTS OF SRESS AND TRAUMA ON FAILURE OF TRANSFER OF PASSIVE IMMUNITY

While there is much left to be understood regarding the specific mechanisms of Ig uptake in the gut of the pre-ruminant calf, it is believed that stress or trauma surrounding parturition is one factor, in particular, effecting the success of transfer of passive immunity (Beam et al., 2009). The birthing process is considerably stressful and traumatic, as a calf is ejected from a controlled, sterile environment, into an adverse, external environment (Murray et al., 2013). Calving can potentially become even more distressing for dam and calf, depending on environmental conditions, such as temperature at the time of calving (Murray et al., 2015a, 2015b, 2015c), untimely or excessively forceful intervention from farm staff (Dufty, 1973), feto-pelvic disproportions, and calf presentation (Mee, 2008; Murray et al., 2013). A cross-sectional study, which surveyed 394 operations in 17 states on their colostrum management practices reported that the odds of FTPI were greater for calves that were not provided a heat source when born during cold-weather months, calves that had experienced dystocia, and those that were born from farms on which the producer did not seek veterinary assistance when unable to position the calf correctly for delivery (Beam et al., 2009).

A common observation is that calf mortality rates, as a result of poor Ig absorption, vary seasonally, due to physical stress associated with temperature (Figure 5) (Olson et al., 1980), with increased mortality rates in mid-winter as well as mid-summer (Martin et al., 1975). These effects are especially severe for calves having experienced dystocia, with reduced resistance to disease, coinciding with increased corticoid levels and inhibited Ig absorption from colostrum (Wiersma et al., 1976; Uetake, 2014).

Figure 5. Mean concentrations (mg/mL) of IgG_1 in serum of cold stressed calves (Group 2) and control (Group 3) calves over time, following consumption of colostrum (Olson et. al, 1980)
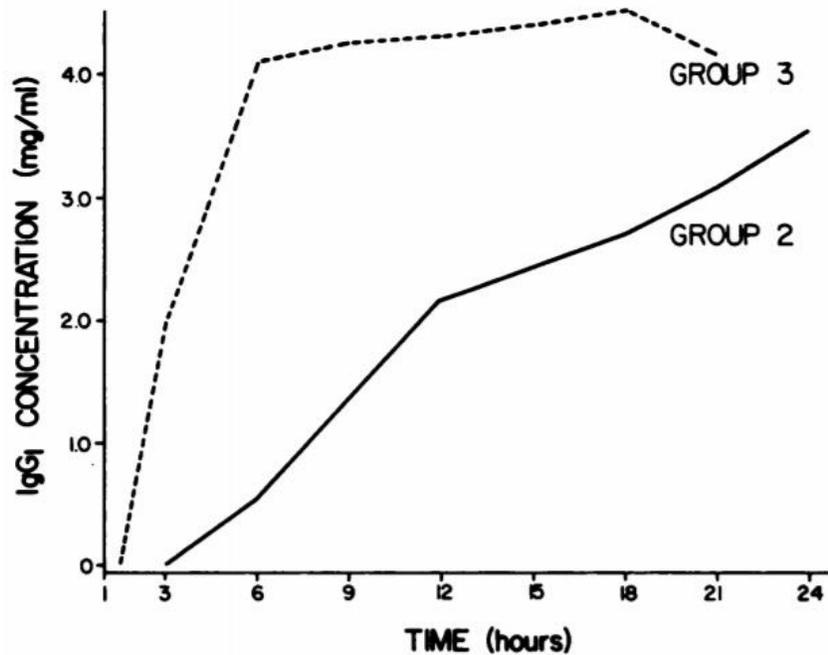
It has even been observed that calves exposed to environmental stressors in utero, such as physical heat stress on the dam during gestation, displayed higher corticosteroid concentrations (Stott, 1979), lower serum IgG concentrations, and lower AEA of IgG (Tao et al., 2012), impairing passive immune transfer. This was likely due to impaired placental development and function associated with heat stress (Tao, 2012), which reduces blood flow to the fetus, and therefore interrupts development of the fetal small intestine, among other observed growth

restrictions (Laporta et al., 2017). Another study found that post-natal respiratory acidosis, a common result of early umbilical rupture or irregular respiration (Murray et al., 2015b, 2015c) due to trauma and asphyxia associated with dystocia (Lombard et al., 2007), disrupted colostral Ig absorption, despite adequate colostrum intake not long after birth (Besser et al, 1990). Finally, a different study found that calves born following dystocia took longer to attain sternal recumbency (**SR**), and those which did not achieve SR within 15 min of birth had reduced AEA of IgG (Murray et al., 2015c).

In addition to the physical stressors listed above, psychological stressors have also been understood to induce an inflammatory response (Kim et al., 2010), which could potentially disturb Ig uptake and the success of transfer of passive immunity. One study, which measured the concentration of specific proteins associated with inflammation surrounding the psychological stress of weaning, found increased levels of cortisol, as well as inflammatory cytokines (Kim et al., 2010), which are signaling molecules excreted from immune cells which promote inflammation. Such an inflammatory response of the cells lining the gut (Soderholm et al., 2001; Hart et al., 2002) due to stress and trauma at the time of calving, may have inhibitory effects on absorption (Peuhkuri et al., 2010) of critical nutrients in colostrum.

MELOXICAM

Traditional protocol for the management of dystocia, or difficult calving, is primarily focused on the assessment of the health of the dam, as opposed to the calf, likely due to the more immediate economic consequences (Murray et al., 2013). Similarly, the majority of studies examining impacts of NSAID treatment surrounding calving have been limited to placental retention or future fertility of the dam (Laven et al., 2012). However, complicated birthing often results in a number of stressful, traumatic, and harmful injuries for the calf as well, including, but

not limited to, fractures, umbilical ruptures (Szenci, 1988), asphyxia, hypoxia (Grove-White, 2000), respiratory/ metabolic acidosis (Szenci, 1982), aspiration pneumonia, hypothermia, edema, or bleeding (Poulsen et al, 2009). Such injuries have the potential to interfere with natural behaviors of the calf, pertinent to survival, such as maintenance of homeostasis (Murray et al., 2015a, 2015b), the ability to stand, move, and suckle colostrum (Mellor et al., 2004).

Meloxicam is an NSAID developed for the treatment of joint disease in humans, such as osteoarthritis and rheumatoid arthritis. The drug has been utilized in horses, rats, humans, dogs, and cats, in order to control inflammation due to injury. These drugs act to inhibit the activity of cyclooxygenase-2 (**cox-2**) (Brideau et al., 2001; Beretta et al., 2005), an enzyme that functions to enhance the production of chemical messengers, which promote inflammation (Hla et al., 1992). When cox-2 activity is blocked by NSAIDs, inflammation is then reduced (Hudson et al., 2008).

Non-steroidal anti-inflammatory drug use in the dairy industry is approved in some countries, not including the United States. In the US, meloxicam is instead an extra-label drug, used under the Animal Medicinal Drug Use Clarification Act (Theurer et al., 2012). According to the American Veterinary Medical Association, extra-label drug use is a term that describes a veterinarian's ability to use an approved drug in a way that is different from the drug's labeling, including for a species, indication, dose, or route of administration that is not listed on the label. In particular, meloxicam is utilized as an effective treatment for neonatal diarrhea, discomfort following dehorning and castration, acute respiratory disease, and acute mastitis (Coetzee et al., 2009), among other indications. However, little scientific evidence exists pertaining to the potential benefits of an NSAID following calving, which may be a contributing factor as to why its use is considerably limited in newborn calves (Murray et al., 2015b).

A study which examined the effect of meloxicam usage in dairy calves at the onset of diarrhea found that those treated with a subcutaneous injection of the drug had improved milk and water intakes when compared to placebo-treated calves. These calves also began consuming starter significantly earlier, displayed faster starter intake rates, and increased BW gain (Todd et al., 2010). The results of this study suggest that meloxicam provides effective relief for inflammation of the gut associated with calf diarrhea.

Several other studies have indicated decreased plasma cortisol levels and behavioral signs of stress in calves administered an NSAID before dehorning and castration, compared to calves not administered the drug. For example, animals that received a single intramuscular injection of meloxicam, in addition to a nerve block, were observed to have had significantly reduced serum cortisol levels (49.7 ± 4.37 nmol/L) for 6 h after dehorning, compared to calves having only received the local block (63 ± 6.94 nmol/L) (Figure 6). These calves also displayed lower heart and respiratory rates in the 24 h following dehorning, reflecting better pain management (Heinrich et al., 2009).

Figure 6. Mean change in serum cortisol concentration of meloxicam and control calves between sham and dehorning (Heinrich, 2009)
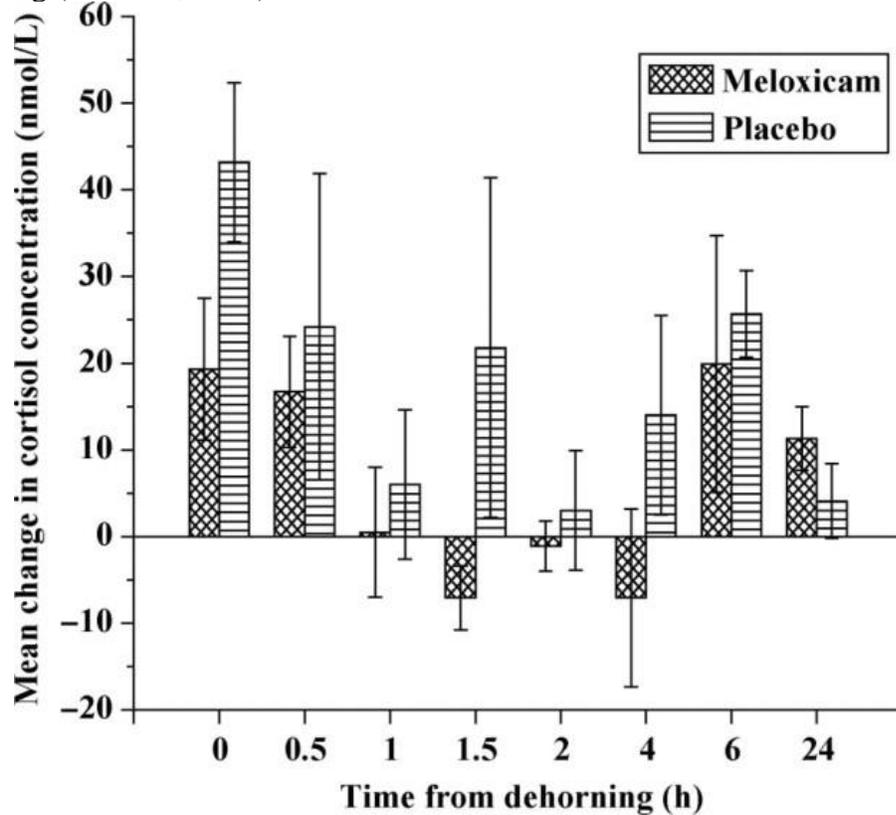
In a separate, similar study, meloxicam-treated calves presented with less ear-flicking and head shaking during the 2 days following dehorning, as well as decreased activity and sensitivity to pressure following dehorning (Heinrich et al., 2010). Calves from another study that were administered meloxicam orally following dehorning were reported to spend more time at the feed bunk on 2 of the 6 days that they were observed, and more time lying down on 4 of the 6 days, as compared to placebo-treated calves (Theurer et al., 2012). These behavioral differences were indicative of an efficient reduction of post-surgical stress. Due to its capabilities of relieving inflammation in the gut associated with diarrhea, as well as decreasing cortisol levels, which have been reported in some studies to be associated with interference of Ig uptake, a

limited number of pilot studies were completed investigating the effect of meloxicam on absorption of colostral Ig and newborn calf health and vigor.

In a study which examined the use of meloxicam in pre-weaned calves following difficult parturition, it was observed that calves assisted at birth, which were administered meloxicam, gained 1.1 kg more in their first week, than did assisted calves given a placebo. Meloxicam-treated calves also had improved health, demonstrated by lower health scores, compared with placebo-treated calves from 0 to 6 weeks of age (Murray et al., 2015b). The same study also analyzed STP as a measure of blood IgG and found that meloxicam treatment was not associated with transfer of passive immunity. However, calves from this study were sampled from 10 commercial farms, and therefore, treatment was inconsistent, indicated by highly variable transfer of passive immunity rates from farm to farm. For example, although consistent with industry standards, calves received colostrum at varying times following birth, ranging from fewer than 2 to 12 h postpartum, and blood samples were collected at varying times, between 24 h to 8 days of age. Furthermore, the quality of the colostrum was not measured. The author of this study included that because STP concentration has been observed to decrease with age, results may be more meaningful if blood collection was to occur at a standardized time following birth (Murray et al., 2015b). In another similar study considering the effect of meloxicam on newborn calf health and vigor, it was observed that calves having received meloxicam treatment following birth displayed significant improvements in vigor and suckling reflex, as well as greater milk intake, compared to calves that received the placebo treatment (Murray et al., 2015a).

There are little published data on the control of pain and inflammation for the calf following birth. Treatment with meloxicam may have the potential to decrease many of the

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physiological disadvantages associated with difficult calving, such as inflammation. If effective, this could, in turn, improve the calf's ability to perform tasks necessary for survival. Conversely, it may also be found that meloxicam has a negative, or insubstantial effect on the inflammatory response of the calf following parturition (Murray, 2015b). In any case, further research is required to determine whether its use may be advisable in certain situations.

CONCLUSION

Of the many areas which can be addressed to improve production and efficiency of a dairy herd, raising calves and heifers is among the most important. Healthy young livestock are more likely to be productive both as heifers, and as the future of the lactating herd (Robison et al., 1988; DeNise et al., 1989). This is because healthy calves are likely to consume more feed as compared to sick calves (Kertz et al., 1984), resulting in greater ruminal VFA production, which in turn promotes more rapid ruminal development (Quigley et al., 1991). As a result, calves and heifers are able to utilize nutrients from feeds more efficiently (Heinrichs, 1993), promoting improved growth performance, and allowing animals to mature at a faster rate. This is beneficial to producers, as heifer-rearing is one of the greatest costs on a dairy farm (Cady et al., 1996). When heifers mature at a younger age, they are able to enter the milking herd in a shorter period of time, minimizing costs for producers (Tozer et al., 2001), and improving profitability of the operation.

Among the most important management strategies for raising healthy calves is the timely feeding of a good quality colostrum (Godden, 2008). Calves should receive 4 L of colostrum with a concentration of at least 50 g/L, as soon as possible after birth (Morin et al., 1997), in order to achieve transfer of passive immunity. Transfer of passive immunity is considered adequate when calves have circulating IgG levels of at least 10 g/L (McGuirk, 2004) at 24 h of

life, or STP levels of 5 g/dL (Weaver, 2000). There are many factors which can interrupt the successful transfer of immunity to the calf via colostrum, including stress surrounding parturition (Beam et al., 2009).

Meloxicam is an NSAID with limited use in livestock in the United States. While a fair amount of research exists pertaining to its benefits as treatment for pain management in calves following dehorning (Heinrich et al., 2009) and castration, as well as for diarrhea (Todd et al., 2010), very few studies have considered its potential for reducing inflammation related to the stress and trauma of parturition, and its effect on Ig absorption. If effective, meloxicam could provide a simple method of improving calf survival, health, and both short and long-term productivity.

CHAPTER TWO

INTRODUCTION

THE EFFECT OF MELOXICAM ON THE ABILITY OF NEONATAL DAIRY CALVES TO ABSORB IGG PROVIDED BY COLOSTRUM REPLACER

Meloxicam is an NSAID approved for use in dairy animals in many countries, excluding the United States, where it can only be prescribed for extra-label use (Theurer et al., 2012). Little scientific evidence exists pertaining to the potential benefits of an NSAID following calving, which may be a contributing factor as to why its use is considerably limited in newborn calves (Murray et al., 2015b). On the contrary, several studies have outlined the use of meloxicam as effective treatment for neonatal diarrhea (Todd et. al, 2010), as well as for pain management surrounding dehorning (Heinrich et al., 2009, 2010; Theurer et al., 2012) among other indications such as castration, acute respiratory disease, and acute mastitis in mature animals (Coetzee et al., 2009).

Calves that were treated with a subcutaneous injection of meloxicam at the onset of diarrhea were observed to have improved milk and water intakes, as well as BW gains compared to placebo-treated calves (Todd et. al, 2010). Moreover, calves that received meloxicam began to consume starter both earlier and at a faster rate than animals in the control group (Todd et. al, 2010). The results of this study are indicative of the efficacy of meloxicam as relief of gut inflammation associated with calf diarrhea.

Moreover, multiple studies which considered the potential of an intramuscular injection of meloxicam, in conjunction with a local block, for minimizing discomfort associated with

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dehorning, indicated positive results when compared with animals which received a nerve block without meloxicam (Heinrich et al., 2009, 2010). In the first of these studies, improved pain management was reflected by lower heart and respiratory rates in the 24 h following the procedure, as well as significantly reduced serum cortisol levels for 6 h after dehorning (Heinrich et al., 2009). In a follow up study, meloxicam-treated calves presented with less ear-flicking and head shaking during the 2 days following de-horning, as well as decreased activity and sensitivity to pressure following dehorning (Heinrich et al., 2010).

Calves from another study that were administered meloxicam orally surrounding dehorning were reported to spend more time at the feed bunk on 2 of the 6 days that they were observed, and more time lying down on 4 of the 6 days, as compared to placebo-treated calves (Theurer et al., 2012). These differences in vital signs, blood parameters, and behavior demonstrate a sufficient reduction of post-surgical stress. Due to its ability to relieve inflammation in the gut associated with diarrhea, as well as to decrease stress and related cortisol levels, which have been reported in some studies to be associated with interference of Ig uptake, research was conducted to investigate the effect of meloxicam on absorption of colostral Ig and newborn calf health and vigor.

Calves that received meloxicam that were assisted at birth gained 1.1 kg more in their first week, than did assisted calves given a placebo. Meloxicam-treated calves also had improved health from 0 to 6 weeks of age (Murray et al., 2015b). Investigators from this study reported that meloxicam treatment was not associated with transfer of passive immunity; however, calves were sampled from 10 commercial farms, and treatment was inconsistent, indicated by highly variable STP concentrations from farm to farm. In another similar study, it was observed that calves having received meloxicam treatment following birth displayed significant improvements

in vigor and suckling reflex, as well as greater milk intake, compared to calves that were not administered the drug (Murray et al., 2013).

There are little published data on the control of pain and inflammation for the calf following birth. Treatment with meloxicam may have the potential to decrease many of the physiological hindrances associated with parturition, such as inflammation. If effective, this could, in turn, improve the calf's ability to perform tasks necessary for survival. Further research is required to determine whether its use may be advisable in certain situations. The objective of the current study were to test the hypothesis: if meloxicam can reduce stress and inflammation of the cells lining the gut following the birthing process, then the ability of the dairy calf to absorb IgG provided by CR will be improved, and these effects will be continued through weaning. Specifically, the purpose was to investigate: 1) if the supplementation of meloxicam improved measures of performance such as IgG uptake, blood ketone concentration, blood glucose, plasma urea nitrogen, skeletal growth, ADG, starter and milk replacer intakes, time for consumption of MR, and feed efficiency, and 2) if there is a difference in effect between administering meloxicam in pill form prior to feeding CR versus powder form mixed in solution.

MATERIALS AND METHODS

Experimental Design

This experiment was reviewed and approved by the University of New Hampshire Institutional Animal Care and Use Committee (Protocol # 180201). It was conducted at the Fairchild Dairy Teaching and Research Center at the University of New Hampshire in Durham, New Hampshire from May to September 2018.

Thirty newborn calves were blocked by expected birth date and randomly assigned to 1 of 3 treatments: (1) CR at 0 h with no meloxicam (control, **CON**), (2) 1 mg/kg meloxicam before

consumption of CR, in pill form (**P**), or (3) 1 mg/kg meloxicam during consumption of CR, crushed and mixed into solution (**S**). A total of 3 experimental units, or 3 calves, each having received 1 of the 3 different treatments, comprised a complete block. Of the 30 calves on study, 5 bulls and 5 heifers received treatment 1, 6 bulls and 4 heifers received treatment 2, and 5 bulls and 5 heifers received treatment 3.

Parturition

Dams were moved to individual maternity pens as they neared calving, and fitted with tail-mounted calving sensors provided by Moocall (Dublin, Ireland) 48 h prior to due dates. Sensors measured tail movement patterns triggered by labor contractions, and a text alert was sent 1 h prior to a predicted calving. Calves born with a Beef Improvement Federation (**BIF**) Calving Ease Score ranging from 1 to 3 were used for this study, meaning calves were born with either no assistance (1), some minor assistance (2), or mechanical assistance (3).

Calves were removed from the dam before nursing and within 30 min of birth, weighed (A and A scales, Prospect Park, NJ) for recording of initial BW, and placed into individual pens (1 x 2.15m). Pens were bedded with kiln-dried sawdust, in a naturally ventilated, enclosed calf room. A blood sample was drawn at 0 h of life, and 1 of 3 treatments was administered. SCCL Gold CR (The Saskatoon Colostrum Company Ltd., Saskatoon, SK, Canada) was prepared by mixing 675 g CR powder in 2.3 L of warm water, to achieve a final volume of 3 L at 22% total solids. This provided calves with a dose of 180 g IgG as soon as possible following birth, and before 1 h.

If calves did not consume the entire volume of CR at birth via nipple bottle, it was kept warm and reintroduced after 1 h. If the remaining CR was refused, it was administered via esophageal tube. A quantity of 10 mL Bar-Guard-99 (Boehringer Ingelheim Vetmedica, Inc.,

Duluth, GA) and 3 mL Calf-Guard (Zoetis, Parsippany, NJ) were provided orally following consumption of colostrum to protect against *Escherichia coli*, bovine rotavirus, and bovine corona virus. Navels were dipped in 7% iodine tincture.

Animal Management

Calves remained on study until 42 days of age. Beginning at 24 h of life, calves were offered milk replacer (Nurture Calf Formula, Professional 24-17 Bov CFL, Provimi North America Inc., Brookeville, OH), free choice starter grain (F4-C15-01-1X TEXT DX CFL HS, Provimi North America Inc., Brookeville, OH) and ad libitum access to water. Following the feeding at 24 h, feeding occurred at 0600 h and 1600 h.

Pens were cleaned and bedded twice daily. Animals were dehorned between 2 and 6 weeks of age via cauterization. Most calves presented with at least minimal diarrhea at some point during the study, typically beginning around 3 weeks of age. Sick calves had body temperatures monitored and were treated with 20-40 g of First Arrival Calf Paste (DBC Ag Products, Lancaster, PA), which includes probiotics and organ compounds to target pathogens that may cause scours. Doses were determined subject to the discretion of the farm's calf manager, based on the severity of symptoms, such as refusal to drink milk replacer, and/ or a sudden drop in starter intake, in addition to diarrhea. Calves that did not respond to initial treatment within 24 h were administered a second bolus of First Arrival Calf Paste. Those with more severe scours and changes in temperament were also given electrolytes orally, and an injection of vitamin B. Incidence of treatment of diarrhea was analyzed following completion of the study.

Feeding, Sampling and Analysis:

Milk replacer was prepared by mixing 216 g powder in 1.8 L warm water. This resulted in a total volume of just over 2 L per feeding, and was fed twice daily. Milk replacer was medicated with Lasalocid (96 g/ton), as well as Diflubenzuron (10.9g/ton) for prevention of development of house, stable, face, and horn flies in manure. Milk replacer contained 24% crude protein (**CP**) and 17% fat (Table 1). The amount of MR fed remained consistent throughout the entirety of the experiment, and refusals were measured at both AM and PM feedings.

Calves were fed a textured, 18% CP starter grain (Table 2), containing whole corn and oats, molasses, and a protein pellet. Starter was medicated with Decoquinate (28.25 g/ton), and Diflubenzuron. Starter fed and refused was measured each morning. Quantity of grain offered was based on grain consumption for the previous day, allowing for a buffer of about 227 g. Additional grain was measured and offered during PM feedings, if necessary. Water offered and refused was measured during every AM feeding, and monitored each afternoon for cleaning and/or addition of more water, if necessary.

Starter and MR intakes were used to analyze total dry matter intake (**DMI**) as well as feed efficiency (**ADG/ DMI**). Samples of starter orts were collected daily and frozen at -20°C for future analysis. Dry matter was determined by thawing frozen samples at room temperature for 12 to 24 h, and drying in paper bags in a forced hot air convection oven (Binder, Bohemia, NY). Samples were dried for 48 h at 55°C.

Skeletal and Blood Sampling and Analysis:

Blood samples were collected using a 10 mL vacutainer tube without additive via jugular venipuncture at 0, 6, 12, 18, and 24 h of age. A single drop of whole blood from 0 h samples was transferred using a disposable pipette to the test strip of a handheld electronic ketone monitoring device (Nova Max Plus, Nova Biomedical, Waltham, MA) for determination of initial blood

ketone concentration. Ketone concentration was measured in duplicate. Samples were allowed to clot before centrifugation at 1,278 x g at 4°C for 20 min. Serum was harvested and frozen for analysis of IgG concentration by Saskatoon Colostrum Company Ltd. following completion of the study, by radial immunodiffusion. Apparent efficiency of absorption at 24 h of age was estimated using the following equation (Quigley et. al, 1998) and adjusted for CR (Cabral et. al, 2015):

$$[(24 \text{ h plasma IgG (g/L)} \times \text{BW (kg)} \times 0.0825) / \text{IgG intake (g/L)}] \times 100.$$

Additional samples were collected weekly for 6 weeks. Calves that were born from Thursday PM until Monday AM were sampled on Tuesday AM, and those born Monday AM until Thursday PM were sampled on Friday PM. During these times, blood samples were collected, and BW measurements, skeletal measurements, and time for consumption of MR were recorded.

Weekly blood samples were collected via jugular venipuncture with a 10 mL vacutainer tube containing no additive for collection of whole blood, and a 10 mL vacutainer EDTA tube for collection of plasma. A small fraction of whole blood was used for analysis of blood ketone concentration using the same methods as the 0 h sample on day 0 of life. The remaining samples from tubes containing the EDTA anticoagulant were centrifuged at 1,278 x g at 4°C for 20 min, and plasma was harvested and frozen for analysis of glucose and PUN following completion of the experiment. Plasma glucose concentrations were measured in duplicate using the Wako Autokit Glucose Assay (Wako Diagnostics, Mountain view, CA), and read on a UV-visible spectrophotometer at a wavelength of 505 nm. Urea concentrations of plasma were measured in duplicate via the diacetyl-monoxime method, and read using a UV/ visible spectrophotometer (Beckman Coulter Inc., Brea, CA) at wavelength of 520 nm.

Body weight (A and A scales, Prospect Park, NJ) and skeletal measurements including, hip height, withers height, length, and heart girth were recorded each week. Body weights were used to calculate average daily gain. Withers and hip heights were collected using a sliding scale height stick with a bubble level. Body length and heart girth were collected using a weight tape. Skeletal measurements were used to calculate gain in cm/day. Time for consumption of MR were documented weekly in seconds.

Statistical Analysis

Unless otherwise stated, data were analyzed as a randomized complete block design with repeated measures, using the MIXED procedure of SAS (SAS Institute Inc., Cary, NC). For analysis of blood metabolites collected in the first 24 h, including rate of IgG absorption, and rate of STP absorption, h was used as the repeated measure. For weekly BW, skeletal measurements and blood metabolites, week was used as the repeated measure. For any variables analyzed with repeated measures, the residual errors are errors within calf across time and represent errors from repeated measurements in the experimental units (calves). Serum IgG, STP, and AEA, analyzed at individual time points (0, 6, 12, 18, and 24 h), as well as final BW and growth measurements collected on day 42 of the study were not analyzed with repeated measures. Planned single degrees of freedom (**df**) contrasts were used to compare the effect of meloxicam versus the control treatment, as well as the administration of meloxicam in pill form, before colostrum, versus powder form, mixed in solution with colostrum. Covariates for all variables included initial BW and sex. Blood ketone concentration at 0 h served as a covariate for analysis of weekly blood ketone measurements, and treatment for the prevention of scours was used as a covariate for analysis of incidence of treatment of diarrhea. Significant treatment and interaction effects were noted at $P \leq$ 0.05, and trends were noted at $0.05 < P \leq 0.10$. Any data points that were 2 standard deviations

from the mean were removed from the data set as outliers. For each of the following models, the random effect of calf within block subclass was used as the error term for the effect of treatment.

For serum IgG, STP, and AEA at individual time points (0, 6, 12, 18, and 24 h), incidence of treatment of diarrhea, as well as for BW and skeletal measurements collected on day 42, the following model was used:

$$Y_{ij} = \mu + B_i + TRT_j + \beta X_{ij} + e_{ij}$$

where Y_i= the dependent variable, μ= the overall mean, B_i= the random effect of the ith block ($i=1,\ldots, 10$), TRT_j= the fixed effect of the jth treatment ($j=1, 2,$ or 3), β= the regression (covariate coefficient), X_{ij}= the covariate measurement, and e_{ij}= the residual error term.

Rate of IgG absorption, and rate of STP absorption were analyzed using the following model:

$$Y_{ijk} = \mu + B_i + TRT_j + H_k + \beta X_{ij} + TRTH_{jk} + e_{ijk}$$

where Y_{ijk}= the dependent variable, μ= the overall mean, B_i= the random effect of the ith block ($i=1,\ldots, 10$), TRT_j= the fixed effect of the jth treatment ($j=1, 2,$ or 3), H_k= the fixed effect of the kth hour of the experiment ($k=0, 6, 12, 18, 24$), β= the regression (covariate coefficient), X_{ij}= the covariate measurement, $TRTH_{jk}$= the fixed interaction between the jth treatment and the kth hour, and e_{ijk}= the residual error term.

Weekly ADG, DMI, feed efficiency, BW, skeletal measurements, and blood metabolites were analyzed according to the following model:

$$Y_{ijk} = \mu + B_i + TRT_j + W_k + \beta X_{ij} + TRTW_{jk} + e_{ijk}$$

where Y_{ijk}= the dependent variable, μ= the overall mean, B_i= the random effect of the ith block ($i=1,\ldots, 10$), TRT_j= the fixed effect of the jth treatment ($j=1, 2,$ or 3), W_k= the fixed effect of the kth week relative to birth, β= the regression (covariate coefficient), X_{ij}= the covariate measurement,

TRTW$_{jk}$= the fixed interaction between the jth treatment and the kth week, and e$_{ijk}$= the residual error term. Degrees of freedom were calculated using the Kenward-Rogers option of the MIXED procedure of SAS.

Covariance structure for each variable was determined based on which of the 5 tested structures resulted in the smallest Bayesian information criterion. Blood glucose, average daily gain, heart girth, and MR intakes were modeled using variance components. Weekly time for consumption of MR, water intake, BW, wither height, hip height, heart girth, length, and gains for withers and length were modeled using Autoregressive 1 covariance structure. Starter intake, total DMI, and feed efficiency were modeled using unstructured covariance. Blood ketone concentrations, PUN and hip gain were modeled using compound symmetry. The only covariance structure tested for the aforementioned variables that was not used was Toeplitz.

Interaction effects of treatment and time were tested in each model, not including those which analyzed specific time points as opposed to repeated measures. Effects of interactions were interpreted by assessing contrasts among different combinations of treatments and time points for significance or trends ($P<0.10$). Variables with significant interaction effects at a particular time point and treatment combination were presented graphically (Figure 2).

RESULTS

All calves achieved serum IgG concentrations $\geq$ 10 g/L, indicating successful transfer of passive immunity. Of the 30 calves on study, 6 calves required feeding via esophageal tube. A total of 4 calves suckled first from the bottle, and then were administered the remainder via esophageal tube, while 2 refused to suckle at all. Of the 4 calves that first suckled and then were tube fed, there was 1 bull that received the control treatment, 1 bull and 1 heifer that received treatment P, and 1 bull that received treatment S. Of the 2 calves that refused to suckle at all,

there was 1 bull that received treatment P, and 1 heifer in that received treatment S. Of all 30 calves, 8 required some level of assistance at birth, not exceeding a BIF calving difficulty score of 3. There were 3 calves that required minor, non-mechanical assistance, one calf which was pulled with chains, and 4 calves that were pulled with a mechanical calf crank. Of the 3 calves that required minor, non-mechanical assistance, there were 2 bulls on treatment P, and 1 heifer on treatment S. The calf which was assisted with chains was a bull on treatment S. Of the 4 calves that were pulled with the calf crank, there were 2 bulls in the control group, 1 bull that received treatment P, and 1 heifer that received treatment S. Of all 30 calves, 26 received treatment for diarrhea. The high incidence of diarrhea within this calf population was likely due to an infection caused by the pathogenic agent, *Cryptosporidium parvum,* as many of the students and farm staff tending to these animals were also infected and diagnosed with *C. parvum*. Of the 26 calves that were medicated for diarrhea, 8 were in the control group, 9 received treatment P, and 8 received treatment S. Of the 30 calves, 5 were treated for the prevention of diarrhea, all of which later presented with scours and were treated at least once more. Of these 5 calves, there was 1 heifer in the control group, 1 bull and 1 heifer that received treatment P, and 2 heifers that received treatment S.

Values for IgG, AEA, and STP, are presented in Table 3. There were no differences among treatments for 24 IgG or AEA. All treatment groups were similar for IgG concentrations, STP, and AEA at 0, 6, and 18 h. At 12 h, serum IgG and AEA differed. At this time point, calves in the control group had greater serum IgG concentration (P=0.01) than calves having been administered meloxicam. Similarly, AEA at 12 h was reduced for calves having received meloxicam compared to those which received the control treatment (P<0.05). No differences were identified among treatments for rate of IgG absorption, or rate of STP absorption. A trend

for a treatment by time interaction was observed at hour 12 for rate of STP concentration (P=0.07), where the control group had STP levels which tended to increase at a greater rate compared to calves having received treatment S (P=0.08) (Figure 2).

There were no differences among treatments in either DMI or MR intakes; however, calves administered meloxicam tended to consume more starter than calves in the control group (P=0.06). There was no effect of meloxicam on water intake, or feed efficiency. A treatment by week interaction was identified for feed efficiency (P=0.02), however, there were no differences at any time points. This was most likely due to a strong effect of week (P<0.01). No differences were observed among treatments on time of consumption of milk replacer.

Values for PUN, glucose, and blood ketone concentrations, and BW are reported in Table 4. Skeletal measurements, and intakes are reported in Table 5. Average initial BW was 44.43 $\pm$ 5.24 kg (mean $\pm$ SD) at birth. Neither average BW, nor final BW was affected by meloxicam treatment. There was a treatment by week interaction for average BW over the duration of the study (P=0.03); however, no differences were identified at any timepoints, therefore, this was likely due to a strong effect of week (P<0.01). Average daily gain was similar among treatments. There was a treatment by week interaction for ADG (P=0.04), with no differences identified at any time points. A strong effect of week (P<0.01) is likely also responsible for this interaction.

All skeletal measurements were similar among treatments. Calves on treatment P tended to have a greater rate of gain in length than calves that received treatment S (P=0.07). A treatment by week interaction was observed for both withers height (P=0.03), and weekly gain in withers height (P<0.01), but no differences were identified at any time points. This was probably due to a strong effect of week for both withers height (P<0.01) and weekly gain in withers height (P=0.02).

There was no effect of meloxicam on PUN concentration. Glucose levels of calves that received meloxicam did not differ from those which received the control treatment; however, calves that received treatment P had lower plasma glucose concentrations than calves that received treatment S ($P<0.05$). Circulating blood ketone concentrations of calves that received meloxicam tended to be greater than calves in the control group ($P<0.10$). A treatment by week interaction was observed for blood ketone concentration, but there were no differences at any time points, so this was likely caused by a strong effect of week ($P<0.01$).

DISCUSSION

No differences were identified among treatments at 24 h for IgG and STP concentrations, or for AEA. These results are consistent with findings from other research (Murray et al., 2015b), in which it was reported that meloxicam treatment was not associated with transfer of passive immunity. Moreover, in the current study, at 12 h post-partum, calves treated with meloxicam were observed to have lower IgG and AEA than those in the control group. While all calves achieved successful transfer of passive immunity, it is possible that meloxicam may have some minor inhibitory effects on uptake of IgG in the gut. These negative effects on Ig uptake were not observed by Murray et al., (2015a, 2015b); however, in those study, meloxicam was administered via subcutaneous injection, rather than orally. Therefore, gastrointestinal consequences of the drug were avoided.

Total DMI, MR consumption, and time for MR consumption were similar among treatments. These findings are supported by a study by Murray et al. (2015a), which reported improved milk intakes ($P=0.04$) in meloxicam-treated calves compared to the control group. While in the current study, this positive effect on milk consumption was not detected, this was to be expected, as calves in the current study were fed just over 4 L of MR per day, while calves in

the aforementioned study were offered up to 8-12 L of milk per day. As a result, the ability to observe such a response in milk intake was limited; however, starter intakes tended to be greater for calves in the current study that were treated with meloxicam compared to those that received the control treatment. These findings are congruous with research by Todd et al. (2010), in which it was reported that calves treated with meloxicam after the onset of diarrhea consumed more starter than calves treated with a placebo ($P<0.01$). It is hypothesized that the anti-inflammatory effects of meloxicam combat functions of pro-inflammatory cytokines, which signal the central nervous system to induce the sickness response, including reduced motivation to seek nourishment (Todd et al., 2010).

Interestingly, meloxicam has a half-life of only 26 h in bovine plasma; therefore, attribution to the drug for improved starter intakes observed over the entire 6-week period is difficult to state. However, Murray et al. (2015a) found that neonatal calves treated with meloxicam had greater improvement in vigor ($P=0.02$), and better health scores from birth to 6 weeks, compared to calves that received a placebo, which could have impacted intakes. Meloxicam-treated calves in the study by Murray (2015a) showed a greater suckling response than placebo-treated animals, which may have improved motivation to drink throughout the pre-weaning period, resulting in greater milk intakes. It is therefore conceivable that healthier, more vigorous calves, are more likely to exhibit vigorous feeding behaviors.

In accordance with improved starter intake, calves in the current study treated with meloxicam also tended to have greater concentrations of circulating ketones. This is expected, as consumption of solid feed results in the establishment of anaerobic microbiota in the gut (Baldwin et al., 2004; Khan et al., 2011). The coupling of both inhabitation of microorganisms in the gut, and increased solid feed intake, initiates the fermentation of fiber and other

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carbohydrates present in solid feeds, and the absorption of VFA (Quigley et al., 1991). As ruminal microbes break down and utilize nutrients from carbohydrates in the feed, less carbohydrate becomes available for digestion after the rumen. Therefore, the amount of glucose available to the animal from the diet declines, and the energy supply of the animal shifts from glucose to volatile fatty acid byproducts of fermentation (Baldwin et al., 2004). During this transitional period of development from pre-ruminant to ruminant, blood parameters for glucose will decrease over time, while BHB, a ketone produced for energy via the metabolism of VFA, will increase (Baldwin et al., 1992).

For this reason, it was anticipated that meloxicam-treated calves would also have lower circulating glucose concentrations, however, this effect was not observed. Instead, no differences were identified between meloxicam-treated calves and those in the control group. On the other hand, calves that received treatment P had lower plasma glucose concentrations than calves that received treatment S. This effect was not observed in analysis of blood ketone concentrations, as results were similar among calves that received meloxicam in pill or powder form.

Another variable response which differed for calves having received different forms of meloxicam treatment was rate of gain in length. Like the results obtained for analysis of glucose, calves that received treatment P tended to havae improved rates of gain in length compared to calves that received treatment S. Differences in effects between form of drug administration could be attributed to residual meloxicam left on the inner surfaces of the bottle when crushed into solution, or differences in the path of the drug within the digestive tract. Specifically, meloxicam first swallowed in pill form is likely to arrive to the rumen, and then pass to the abomasum, while meloxicam crushed into solution with CR is more likely to bypass the rumen as a consequence of the reflexive closure of the esophageal groove in response to milk.

Treatment with meloxicam did not affect skeletal measurements, BW, or ADG. These results were similar to those from both studies by Murray et al. (2013, 2015a). In the first of those studies, ADG did not differ in calves treated with meloxicam compared to the control. In the second study, 6-week weight gain was also unaffected by meloxicam treatment. However, calves that were assisted at birth and treated with meloxicam were observed to gain more weight in the first week compared to assisted placebo-treated calves. Notably, the opposite effect was observed in calves that received meloxicam but were not assisted at birth. These results indicate that while meloxicam may benefit calves born from difficult parturition, it might not have such positive impacts on calves that do not suffer substantial inflammation following birth. Alternatively, such variable results may also suggest that weight gain could be a poor indicator of efficacy of NSAID use in calves (Murray et al., 2015b).

Meloxicam usage did not affect incidence of treatment for diarrhea. These results are congruous with those of another study which considered the effects of injectable meloxicam on symptoms of neonatal diarrhea (Todd, 2007). While later research did report improvements in milk intake, as well as earlier starter intake for meloxicam-treated calves compared to those having received a placebo injection (Todd et al., 2010), investigators reported that these effects were not due to a variation in duration of illness, as meloxicam-treated animals and those having received a placebo did not differ in time to resolution of abnormally soft stools.

The use of meloxicam for treatment of inflammation following birth offers promising results for improvement of starter intake and ruminal development, evidenced by blood ketone values. Further, administration of the drug in pill form may be more beneficial for growth and rumen development compared to powder form, mixed in solution with CR. In the current study, this was indicated by improved rates of gain in length and lower glucose values for calves that

received the drug as a pill, as opposed to a powder in solution with CR. Further research is

necessary to confirm these observations.

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IACUC #: 180201
Project: The Effect of Meloxicam on the Ability of Neonatal Dairy Calves to Absorb Nutrients Provided by Colostrum Replacer
Approval Date: 22-Feb-2018

The Institutional Animal Care and Use Committee (IACUC) reviewed and approved the protocol submitted for this study under pain or distress category C - *the research potentially involves minor short-term pain, discomfort or distress which will be treated with appropriate anesthetics/analgesics or other assessments.*

Approval is granted for a period of three years from the approval date above. Continued approval throughout the three year period is contingent upon completion of annual reports on the use of animals. At the end of the three year approval period you may submit a new application and request for extension to continue this project. Requests for extension must be filed prior to the expiration of the original approval.

Please Note:
1. All cage, pen, or other animal identification records must include your IACUC # listed above.
2. Use of animals in research and instruction is approved contingent upon participation in the UNH Occupational Health Program for persons handling animals. Participation is mandatory for all principal investigators and their affiliated personnel, employees of the University and students alike. Information about the program, including forms, is available at
http://unh.edu/research/occupational-health-program-animal-handlers.

If you have any questions, please contact either Dean Elder at 862-4629 or Julie Simpson at 862-2003.

For the IACUC,

Jessica A. Bolker, Ph.D.
Chair

cc: File

Table 1. Nutrient analysis of milk replacer

Item	DM (%)	
CP	25.48	$\pm$ 0.51
FAT	16.35	$\pm$ 1.65
ASH	6.97	$\pm$ 0.16

Table 2. Nutrient analysis of calf starter

Item	DM (%)
CP	22.85
ADF	8.79
NDF	16.41
FAT	3.75
ASH	8.16
CALCIUM	1.18
PHOSPHORUS	0.68
MAGNESIUM	0.41
POTASSIUM	1.25
SULFUR	0.25

Table 3. Immunoglobulin absorption of calves supplemented with no meloxicam, meloxicam as a pill, or meloxicam mixed into solution with CR

Item	Treatment[1]				P-value[2]		
	CON	P	S	SEM	MELvCON	PvS	TRTxTIME
Rate IgG, (g/L)/h	0.96	0.96	0.97	0.06	0.89	0.93	0.55
IgG 6 h, g/L	15.89	14.26	16.96	1.42	0.87	0.18	-
IgG 12 h, g/L	28.47	24.4	22.59	1.85	0.01	0.47	-
IgG 18 h, g/L	25.85	24.32	23.53	1.36	0.2	0.67	-
IgG 24 h, g/L	24.12	23.15	23.11	1.67	0.54	0.98	-
Rate STP, (g/dL)/h	0.05	0.05	0.04	<0.01	0.15	0.62	0.07
STP 6 h, g/dL	5.25	5.1	5.15	0.14	0.43	0.78	-
STP 12 h, g/dL	5.7	5.58	5.52	0.08	0.13	0.58	-
STP 18 h, g/dL	5.72	5.66	5.53	0.09	0.28	0.34	-
STP 24 h, g/dL	5.71	5.61	5.65	0.1	0.54	0.74	-
AEA[3] 6 h, %	29.47	25.41	30.36	2.73	0.64	0.22	-
AEA 12 h, %	56.09	47.54	43	2.8	<0.01	0.25	-
AEA 18 h, %	48.52	45.16	42.95	2.32	0.12	0.49	-
AEA 24 h, %	47.63	45.94	48.73	3.21	0.94	0.55	-

[1]Treatments: CON- 0 mg/ mL meloxicam, P- 1 mg/kg meloxicam before consumption of CR in pill form, S- 1 mg/kg meloxicam during consumption of CR, crushed and mixed into solution
[2]single df contrasts were used to compare the effect of meloxicam versus the control, as well as P versus S
[3]Apparent Efficiency of Absorption (AEA): [(24 – h plasma IgG (g/L) x BW (kg) x 0.0825) / IgG intake (g/L)] x 100 (Quigley et. al, 1998; Cabral et. al, 2015)

Table 4. Blood metabolites and intake, BW, of calves supplemented with no meloxicam, meloxicam as a pill, or meloxicam mixed into solution with CR

| | Treatment[1] | | | | P-value[2] | | |
Item	CON	P	S	SEM	MELvCON	PvS	TRTxTIME
GLU, mg/dL	80.02	73.2	83.26	3.54	0.67	<0.05	0.83
PUN, mg/dL	5.64	5.94	6.39	0.41	0.3	0.46	0.35
Blood ketone, mmol/L	0.12	0.15	0.17	0.02	0.09	0.49	<0.05
Starter intake, g/d	452.59	560.38	515.43	37.02	0.06	0.4	0.46
MR intake, g/d	426.09	426.36	426.77	0.35	0.29	0.41	0.83
Total DMI, g	884.41	995.51	917.97	44.29	0.18	0.21	0.92
MR consumption time, s	75.54	65.98	65.44	9.32	0.39	0.97	0.47
Free water intake, kg	1.55	1.31	1.61	0.18	0.71	0.27	0.94
BW, kg	50.7	51	50.67	51	0.91	0.81	0.03
Final BW, kg	61.72	59.61	63.39	1.66	0.9	0.13	-
ADG, kg/d	0.38	0.43	0.45	0.35	0.16	0.75	0.04
ADG/DMI	0.41	0.37	0.46	0.46	0.91	0.25	0.02

[1]Treatments: CON- 0 mg/ mL meloxicam, P- 1 mg/kg meloxicam before consumption of CR in pill form, S- 1 mg/kg meloxicam during consumption of CR, crushed and mixed into solution
[2]single df contrasts were used to compare the effect of meloxicam versus the control, as well as P versus S

Table 5. Skeletal measurements, and performance of calves supplemented with no meloxicam, meloxicam as a pill, or meloxicam mixed into solution with CR

	Treatment[1]				P-value[2]		
Item	CON	P	S	SEM	MELvCON	PvS	TRTxTIME
Withers height, cm	83.91	83.36	82.56	0.53	0.15	0.3	0.03
Withers height rate of gain, cm/d	0.15	0.18	0.15	0.01	0.58	0.12	<0.01
Final withers height, cm	86.65	86.93	86.06	0.37	0.75	0.12	-
Hip height, cm	87.52	87.33	86.69	0.49	0.4	0.37	0.45
Hip height rate of gain, cm/d	0.15	0.18	0.15	0.18	0.2	0.13	0.94
Final hip height, cm	90.48	90.9	90.09	0.46	0.97	0.23	-
Length, cm	67.68	67.01	67.6	0.43	0.47	0.35	0.59
Length rate of gain, cm/d	0.19	0.24	0.19	0.24	0.33	0.07	0.58
Final length, cm	72.19	72.04	72.41	0.8	0.97	0.75	-
Heart girth, cm	86.03	86.01	85.14	0.4	0.36	0.14	0.85
Heart girth rate of gain, cm/d	0.17	0.16	0.19	0.02	0.99	0.37	0.94
Final heart girth, cm	90.36	90.01	90.22	0.87	0.78	0.86	-
Incidence of treatment for diarrhea	1.38	1.16	1.45	0.29	0.83	0.5	-

[1]Treatments: CON- 0 mg/ mL meloxicam, P- 1 mg/kg meloxicam before consumption of CR in pill form, S- 1 mg/kg meloxicam during consumption of CR, crushed and mixed into solution
[2]single df contrasts were used to compare the effect of meloxicam versus the control, as well as P versus S

Figure 1. Rate of serum IgG concentration at 6, 12, 18, and 24 h
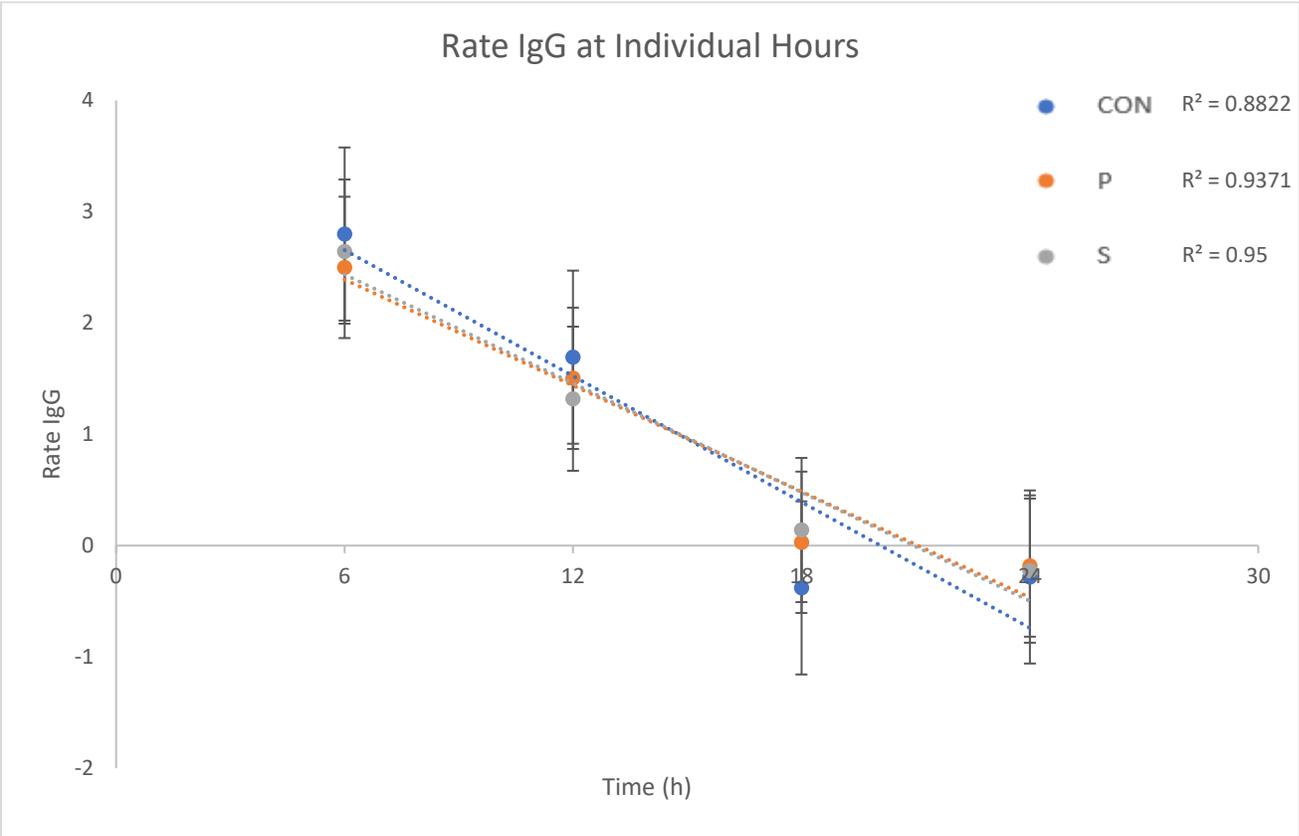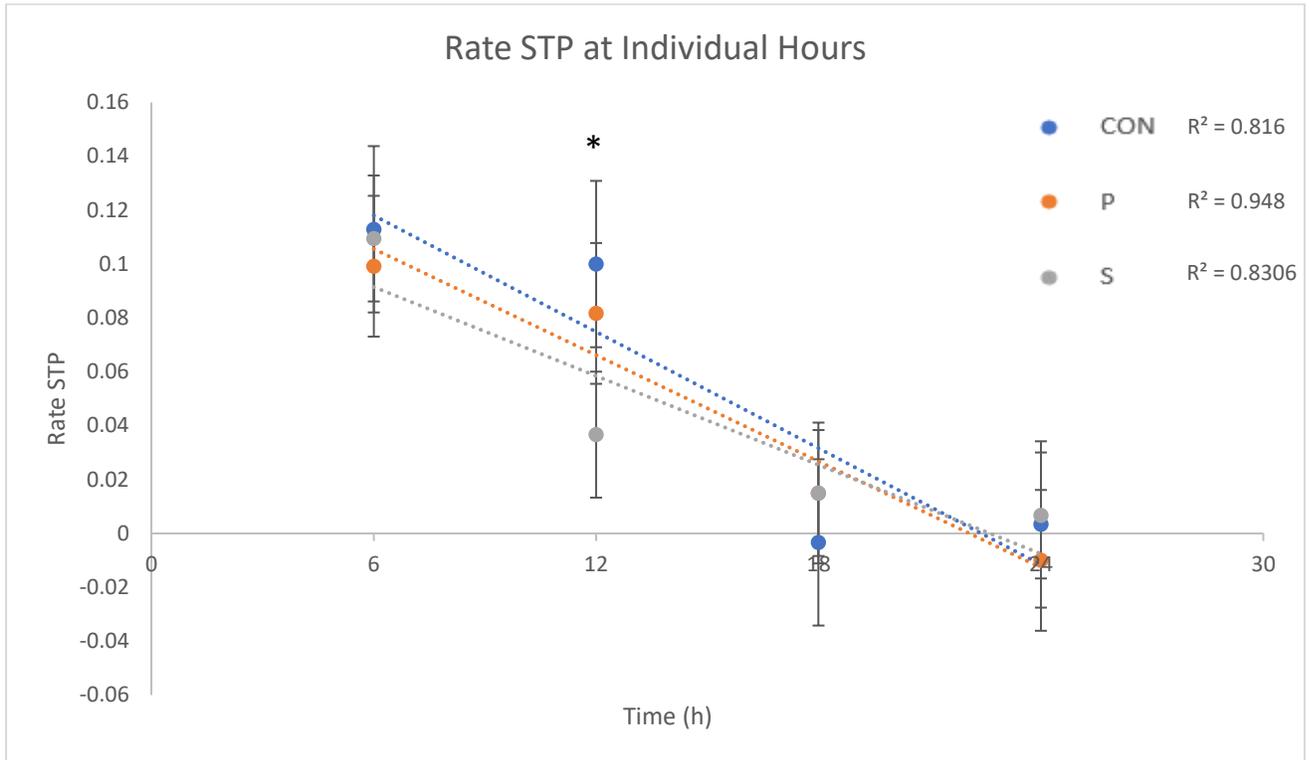
Figure 2. Rate of serum total protein concentration at 6, 12, 18, and 24 h

*A trend for a treatment by time interaction was observed at h 12 for rate of STP concentration (P=0.07), where the control group had STP levels which tended to increase at a greater rate compared to calves having received treatment S (P=0.08)