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Review Article

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Post-operative Pain and its Management in Local Breed Sheep: A Review

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Abstract

Most of the surgical procedures can be performed safely and efficiently in ruminants using a combination of physical restraint, mild sedation and local anaesthesia. Postoperative pain is managed using analgesia. Effective post-operative pain management in sheep should be combining the reduction of primary and acute pain with the prevention of secondary (central or peripheral) hypersensitivity. NSAID include a variety of different agents of different chemical classes. Most of these drugs have three major types of effect such as anti-inflammatory, analgesic and antipyretic effect. The first two are essential for pain management: anti-inflammatory effect–modification of the inflammatory reaction and analgesic effect–reduction of some types of pain. All of these effects are related to the primary action of these drugs: cyclo-oxygenase enzymes inhibition, reducing inflammation by decreasing the production of prostaglandins, tromboxane A2 and other inflammation mediators. Meloxicam is a NSAID derived from oxicam. Meloxicam acts by inhibition of prostaglandin synthesis exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects. Treatment with meloxicam reduces local swelling, inflammation and pain by inhibiting cyclooxygenase enzyme, which is the rate-limiting enzymatic activity in the conversion of arachidonic acid to pro-inflammatory prostaglandins. This effect was greatest at 8 hours of administration. Meloxicam levels gradually increased over time at the inflamed site.

Keywords: Acute pain, Chronic pain, Local breed sheep, Post operative pain

Introduction

The recognition of pain in sheep and other farm animals has lagged behind that of companion animals, horses and humans. However, pain research in sheep has been increasing over the past 15-20 years (Hudson *et al*., 2008). As part of good animal welfare, the freedom from pain, injury and disease is just one of the 5 freedoms outlined by the Farm Animal Welfare Council (2009). According to the International Association for the Study of Pain's (IASP) (1994), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Surgical incision is potential cause of pain because there is activation of peripheral nociceptors from tissue damage or trauma. Nociception is the unconscious afferent activity produced in the peripheral and CNS by stimuli that have the potential to damage tissues (Raja *et al.*, 1999).

According to Fonda (2009), pain is classified as acute, inflammatory, chronic and neuropathic pain. Animals depend on ability to respond to challenges coming from injury and pain; the only way available to receive and convey this information to the central nervous system (CNS) is through sensory organs distributed all over the body. Neurons have evolved specialized properties that allowreceiving information, process and transmitting it into other cells (Julius and Basbaum, 2001).

Pain assessment method in animals can generally be categorized into objective and subjective methods. Objective method is instrumental and more reliable than subjective method. Subjective methods are observations and categorizations of behaviours and can be measured in the form of scales, such as gait scoring scale for locomotion. It is more prone to poor reliability because it is non instrumental and the evaluation differs between individual observers (Weary *et al.*, 2006). A combination of objective and subjective methods may be optimal to gain more insight on what the animal is experiencing (Dobromylskyj *et al.*, 2005).

Pain is essentially a subjective experience and so it is very difficult to directly assess it, even in humans (Broom and Johnson, 2000). Whereas it is possible to assess pain in humans directly usually using a rating scale scored by the subject; this is impossible in animals (Herr *et al*., 2006). Indirect symptoms that can serve as indicators for assessment of pain in animals include changes in physiological and behavioural parameters and total and differential leukocyte count (Molony and Kent, 1997).

Post-operative pain assessment and management in sheep has been challenging perhaps due to stoic nature, as an adaptation selected to skin their signs of pain or discomfort without complaint. Since sheep can be relatively undemonstrative when hurt (Anil *et al.*, 2005; Dobromylskyj *et al.*, 2005; Hudson *et al.*, 2008). Effective management of pain in sheep using meloxicam, non-steroidal anti-inflammatory drugs, has combining result for reduction of inflammatory pain and acute pain with the prevention of secondary hypersensitivity and chronic pain (Nolan, 2000). To date, there are no works done related to the effect of meloxicam in animals' pain relief within the country. Several surgical procedures may severely affect the welfare of farm animals. These procedures generally influence welfare by causing short or long term pain which is underestimated by veterinarians and practitioners. Therefore, the objectives of this review is: to review the effect of meloxicam to decrease postoperative pain in local breed sheep.

Pain Mechanism in Animals

According to the International Association for the Study of Pain's (IASP) (1994), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Similarly, Broom and Fraser (2007) have defined it as "pain is an aversive sensation and feeling associated with actual or potential tissue damage". Other definition include that pain is "an aversive sensory and emotional experience representing awareness by the animal of damage or threat to the integrity of its tissues" (Molony and Kent, 1997).

Laparotomy, castration, dehorning and tail docking are mutilations that cause tissue damage and pain. In the context of surgical mutilations pain can be divided into three main stages. Firstly, pain perception at the time of surgery, where pain receptors transmit nerve impulses to the brain where are translated into the actual feeling of pain. Unless the animal has been anaesthetised in some way (general or local anaesthesia), it will try to escape but it is usually restrained. Secondly, over the next few days, the body normally repairs the damage by mounting an inflammatory response and this too can be painful due to the release of local tissue substances such as prostaglandins. Pain at this stage can be alleviated by the use of anti-inflammatory drugs. Moreover, unless the impulses in pain pathways are modulated or blocked at the time of injury, pain becomes exaggerated through a process known as 'wind-up', where not only the injured site but also adjacent sites become more sensitive (hyperalgesia) and even non-painful stimuli can become painful (allodynia). It is important to give some form of pain relief at the time of surgery as well as for a few days after surgery to avoid wind-up. Thirdly, while normally successful healing occurs unless there is infection but occasionally pathological changes occur and painful growth at the end of the cut nerves neuronal has been recorded in some species (Broom and Fraser, 2007).

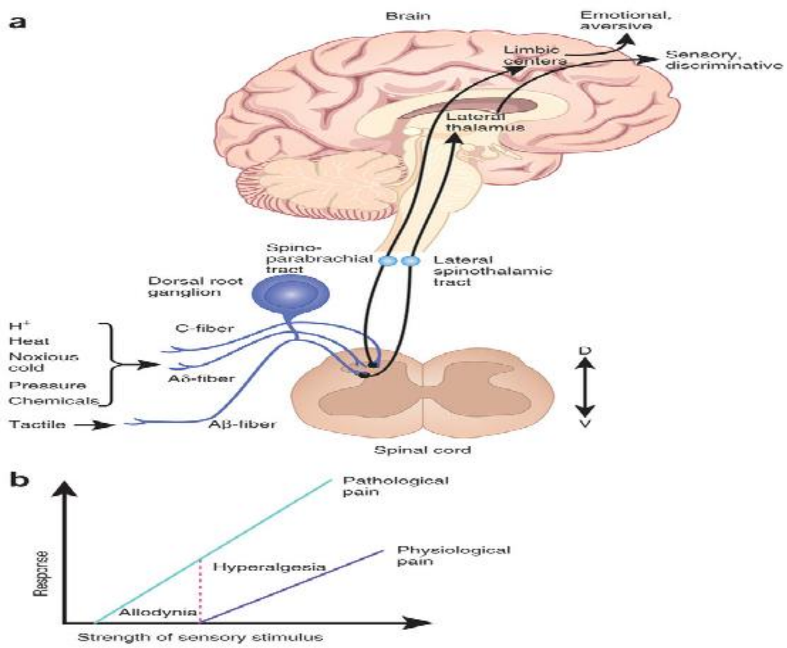

Fig. 2: Pathological and physiological pain in animals

The tissue damage and the inflammatory response produce various chemicals or sensitizers such as potassium ions, prostaglandins, histamine, bradykinin, nerve growth factor, cytokines and chemokines, which are involved in the activation of the peripheral nociceptors. Animals depend on their ability to respond to challenges coming from the environment and other animals. The only way available to receive and convey this information to the CNS is through sensory organs distributed all over the body. Neurons have evolved specialized properties that allow them to receive information, process and transmit it to other cells. The stimuli translated into nerve impulses are: incisional pain, light, pressure, chemicals, temperature, vibration and sound waves. Sensory reception begins in receptor cells, that are specialized to respond to particular kinds of stimuli and transmitted through a corresponding nerve fibre (afferent neurons) to the CNS to processed (Anderson and Muir, 2005a).

Surgical incision is potential cause of pain because there is activation of peripheral nociceptors from tissue damage or trauma. Nociception is the unconscious afferent activity produced in the peripheral and CNS by stimuli that have the potential to damage tissues. Although many authors assert that nociception should not be confused with pain, which is a conscious experience, others say it is the first and basic part of the pain mechanism. Nociception mechanism depends essentially on two stages: the first stage is transduction, in which the noxious stimuli such as incisional pain are translated into electrical activity (Raja *et al.*, 1999). This occurs at the sensory endings of special nerve fibres termed “nociceptors”. The second stage transmission which is the propagation of the electrical impulses throughout the sensory nervous system to the CNS. Glutamate is the predominant excitatory neurotransmitter in all nociceptors (Julius and Basbaum, 2001).When a noxious stimuli is induced it causes a “first pain”, also termed “physiologic pain”, that serves a protective biological function by acting as a warning of potential tissue damage. This is an almost instant transmitted sensation that travels through thinly myelinated Ad fibres (Clark *et al.*, 1997; Carr and Goudes, 1999).

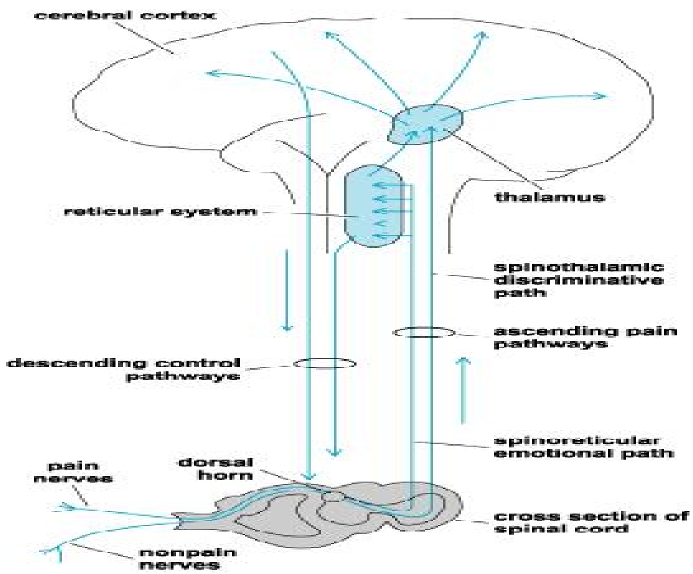

Fig. 3: Ascending and descending pain pathways

Types of Pain

Surgical pain may arise from surgical incision on a variety of muscle tissue types and it is often classified into inflammatory pain, neuropathic pain, acute and chronic pain (Fonda, 2009). However, looking to the scope of this study the review is restricted to inflammatory and acute pain subchapters.

Inflammatory pain

Painful states are caused particularly by tissue or nerve damage, inflammatory processes, viral infections or demyelination are characterized by pain hypersensitivity (Vinuela-Fernandez *et al*., 2007). Somatic pain originates in the skin known as superficial pain. If it originates in the muscles, bones, joints or connective tissues is called deep pain. In other words somatic pain refers to pain originating from the periphery and can be in most cases being well localized. Visceral pain arises from viscera (Joshi and Gebhart, 2000). The sensitivity of viscera to mechanical, thermal or chemical stimuli is very different. Viscera are predominantly sensitive to distension of hollow muscular-walled organs and to inflammatory processes. Visceral pain can be referred to another part of the body (Julius and Basbaum, 2001). Information from certain regions of viscera converges on spinal cord neurons and pathways that convey information from somatic structures (Frandson *et al.*, 2009). Visceral pain is usually described as more diffuse and unpleasant than somatic pain (Hellyer *et al*, 2007; Wilson, 2008; Paine *et al*., 2009).

Visceral pain also differs from somatic pain with regard to localization. Visceral pain is perceived as being extensive and diffuse and is often associated with a sense of nausea and malaise. Referred pain, whereby the pain response is localized to distant structure, is another hallmark of visceral pain (Fonda, 2009; Li *et al.*, 1999). Visceral pain is unique in that there are no first (fast) and second (slow) components. This pain is often poorly localized, deep and dull (Gebhart, 1996). It is usually triggered by other kind of stimuli, namely stretching, compression or ischemia. Tactile nerve fibres (Ab fibres) detect innocuous stimuli applied to skin, muscle and joints and thus do not contribute to pain. However, some of these fibres are connected with interneuron linked to descending noxious stimuli inhibitory paths and so stimulation of large Ab fibres can reduce pain, as occurs when you activate them by rubbing the area near a wound. This may explain why animals tend to lick or scratch painful spot's surrounding area. The idea of different ascending and descending nerve fibres interacting and influencing the nociceptor transmission led to the theory called "the gate control theory of pain" (Anderson and Muir, 2005a; Melzack and Wall, 1995).

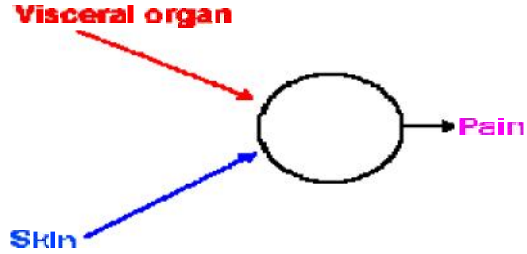

Fig. 4: Somatic and visceral pain

Acute pain

Acute musculoskeletal injuries are characterized by localized tissue swelling, inflammation and pain. Acute pain is the pain accompanying some form of tissue damage or trauma, and is usually considered to last a few days after the event. A much-studied model of acute pain is that accompanying surgery. Typically surgery is accompanied by severe acute pain in the first few days after surgery, with pain being spontaneous, ongoing or evoked by movement (coughing, mobilization). The pain is usually most severe on the first and second day after surgery, gradually decreasing thereafter to usually disappear at least in its spontaneous or ongoing form at the end of the first postoperative week. In a recent study of major surgical interventions 43%, 27% and 16% of patients experienced significant spontaneous or ongoing pain on postoperative days 1, 2 and 3, respectively (Honore *et al*., 2000; Svensson, 2000; Eicher *et al.*, 2006). For any type of pain ongoing or evoked the respective incidences of significant pain for postoperative days 1, 2 and 3 were 88%, 81% and 72%. This indicates that acute pain decrease as increase postoperative days. In reviewing the literature, major postoperative pain appears to be present in between 30-70% of surgical patients, with at least 20% achieving inadequate pain relief overall (Pogatzki-Zahn*et al*., 2007). Unfortunately, it has to be noted that acute postoperative pain management has not improved over the last decade despite a variety of concerted attempts at improvement during this period (Henke and Erhardt, 2001; Apfelbaum *et al.*, 2003; Mogil and Crager, 2004; Leung and Cahill, 2010).

Acute pain soon disappears once the damaged tissue has been healed. In contrast, chronic or persistent pain lasts beyond the expected healing time for an injured tissue and can be more difficult to recognize, because it is not possible to identify behaviour that would uniquely and reliably indicate the existence of chronic pain (Mogil and Crager, 2004). It is also important to realize that various tissues and organs of the body can have different sensitivities to painful stimulation. For example, mucous membranes, cornea or dental pulp are considered to be extremely sensitive, whereas, parenchymatous organs are characterized as less painful (Henke and Erhardt, 2001; Lamont *et al*., 2000).

Acute pain has a biologically adaptive function by facilitating tissue repair and healing. This is achieved by hypersensitizing the injured area (primary hyperalgesia) as well as the surrounding tissues (secondary hyperalgesia) to all type of stimuli such that contact with any external stimulus is avoided and the reparative process can proceed. After surgery, there are many variable reactions at the different levels of the nervous system. Among systemic effects, it is possible to identify supraspinal or segmental: consists in an increased sympathetic tone accompanied by peripheral vasoconstriction, increased cardiac output, myocardial work and skeletal muscle tone and decreased gastrointestinal and urinary tone (Aasvang *et al*., 2008; George, 2003; Lamont *et al*., 2000).

Pain Assessment Methods

Pain assessment methods in animals can generally be categorized into objective and subjective methods (Weary *et al*., 2006).

Objective method

Objective method is instrumental and more reliable method. This method is measuring physiological parameters including heart rate, respiration rate, temperature; and hematological parameters like total and differential leukocyte count; stress response and daily activity or behavioural parameters such as feed intake, body weight gain and water intake. It is important method to avoid individual errors during observations (Weary *et al*., 2006). All these parameters were included in this study except body weight gain and measured individually based on instruments they needed.

Subjective method

Subjective method is observations and categorizations of certain behaviours and postures and can be measured in the form of scales, such as the gait scoring scale for lameness, but is more prone to poor reliability because the evaluation differs between observers (Weary *et al*., 2006). Behavioral subjective methods can become a form of objective measure if used in a quantifiable way that is repeatable and reliable, especially with experience and training of the observers. These behavioural measures can be quantified to create objective measures that will give insight into changes in behaviours. For example, lame dairy cattle spend more time lying and less time feeding per day (Galindo and Broom, 2002). A combination of objective and subjective methods may be optimal to gain more insight on what the animal is experiencing. The observation of behaviors to interpret what the animal is experiencing is important in pain assessment (Dobromylskyj *et al.,* 2005).

Although it is possible to use behavioural responses to painful stimuli for assessment of pain in animals these indices have certain limits. Firstly, the validation and recognition of changes in behaviours related to pain are depending on the training and experience of the observer and any person who uses behavioural parameters should be to a certain extent familiar with the personality of the animal that is subjected to pain assessment. Secondly, responses of various species to the same procedure can differ considerably. Thirdly, even individual animals of one species can show significant differences in responsiveness to painful stimulation as is the case in humans. This is known in ruminants, horses, dogs, cats and primates and it is believed that it can occur in other species. As a possible solution, the estimation of pain using behavioural indices should involve discussion and agreement in methods and training of the person who carries out the observation so that they can recognize and distinguish abnormality and normality (Bufalari *et al*., 2007).

Indicators of Pain in Animals

Pain is essentially a subjective experience and so it is very difficult to directly assess it, even in humans (Broom and Johnson, 2000). Whereas it is possible to assess pain in humans directly usually using a rating scale scored by the subject; this is impossible in animals (Herr *et al*., 2006). Indirect symptoms that can serve as indicators for assessment of pain in animals include changes in physiological and behavioural parameters and total and differential leukocyte count (Molony and Kent, 1997).

Physiological parameter assessment

Physiological parameters including: heart rate, body temperature and respiratory rate are important to pain assessment in animals (Price *et al*., 2003). When veterinarians were askedthathow pain is recognized in animals? The most frequent answers were the physiological parameters, like heart rate, rectal temperature and respiratory rate have been tested several times during the study periods. Increasedphysiologicalparameter such as heart rate, rectal temperature and respiratory rate is often seen as an indicator of mild to severe pain in animals (Pritchett *et al.*, 2003).The evaluated increased heart rate, respiratory rate and rectal temperature are a potential indicator of postoperative pain in animals after abdominal surgery. Body temperature was chosen because elevation (fever) can be caused by inflammation of the incisional area, which may cause pain. Subsequently swelling of the incisional area can give an impression of the extent of inflammation (Price *et al*., 2003).

Heart rate has increasingly been applied in veterinary research related to surgical pain, inflammation and pathological conditions. Heart rate represents the net interactions between vagal which reduces heart rate and sympathetic which increases heart rate regulation (Hainsworth, 2005). At rest, vagal regulation dominates whereas increasing physical activity is frequently characterized by decreasing vagal and increasing sympathetic influences. A rise in heart rate is mainly caused by an increase in sympathetic activity but it may also result from a decrease in vagal regulation or from simultaneous changes in both regulatory systems. Separate effects of the two branches of the autonomic nervous systems cannot be determined by simple addition or subtraction of the relative components (Borel and Von, 2007).

Leukocyte count assessment

The total numbers of white blood cells are called leukocytes. The major function of leukocyte is to defend the body against organisms and injury. Leukocytes are the main players in pain, inflammatory and immune responses. The inflammatory process is triggered by cell injury, which can be caused by a variety of conditions such as trauma, burns, ischemia, surgery, snakebite, caustic chemicals and extremes in heat and cold as well as infectious microorganisms. Surgical incisions would be the most common to trigger inflammation by increasing inflammatory mediators. Any damage to the vascular endothelium or mast cell will trigger an inflammatory response, which is orchestrated by inflammatory cytokines. Cytokines are hormone like protein mediators responsible for the cell to cell communication that regulates local and systemic physiologic and pathologic interactions. The cells of the vascular endothelium have been recently identified as a major player in the inflammatory process (Catalano, 2002).

Differential leukocyte count is determination of the proportion of absolute count per unit volume of defined classes or subsets of leukocytes in the blood sample. The purpose of differential leukocyte count is to obtain the picture of the true distribution of the leukocyte in the peripheral blood. This is used by clinician to determine the disease status of patients. The leukocytes present in the peripheral blood are composed of five types of mature cells. A common manner in which WBCs are divided is by the presence of granules in the cytoplasm (Nasar *et al*., 2002). WBCs that contain granules in their cytoplasm including neutrophils, eosinophils, and basophils are known as granulocytes. These granules contain biochemical mediators that serve inflammatory and immune functions. Granulocytes also contain enzymes in their cytoplasm capable of destroying microorganisms and catabolizing debris ingested during phagocytosis. Itdevelops in the bone marrow, circulate in the blood stream. However, WBCs that do not have granules such as monocytes and lymphocytes are known as non granulocytes (Sadovsky, 2000; Aegwanich *et al*., 2009).

Neutrophils are mature granulocyte that account for more than half of all the WBC subtypes in circulation. It is called segmented neutrophils or polymorphonuclear neutrophils because the nucleus of these cells consists of 3 to 5 lobes connected by thin strands (Barrington and Parish, 2001; Meyer and Marrow, 2004). Highly motile, these cells are the first to arrive within 90 minutes in response to acute inflammation or infection; they migrate out of the capillaries into the inflamed tissue site in a process called emigration. The neutrophils ingest microorganisms and debris and then die, forming purulent exudates, which is removed by the lymphatic or through the epithelium. There is an increased demand for neutrophils, as response to acute pain; immature neutrophils may be released from the bone marrow. These cells have unsegmented nuclei that resemble bands/ rods are known as band neutrophils. They are normally found only in very low percentages in circulating blood (Scott *et al*., 2006; Naskalski *et al*., 2007).

Eosinophils function principally to ingest and kill multi-cellular parasites. It is effective in detoxifying antigen-antibody complexes during allergic reactions. People with chronic allergic conditions such as atopic rhinitis and extrinsic asthma typically have elevated circulating eosinophil counts (Catalano, 2002). Eosinophils are believed to play a role in down regulating hypersensitivity responses by neutralizing histamine, inhibiting mast cell degranulation, and inactivating slow-reacting substances of anaphylaxis. Basophils are associated with systemic allergic reactions. Similar to mast cells, basophils have granules that contain proinflammatory chemicals such as histamine, serotonin, bradykinin, and heparin. Itreleases their granules in response to stimulation by immune cells. Basophils circulate in the blood stream, whereas mast cells are found in connective tissue. The average basophil has a life span of days, but the mast cell can live weeks to months (Catalano, 2002; Fekete and Kellems, 2007).

Monocytes are the largest of the WBCs and are young cells found freely circulating in blood or route to a tissue location. Once the young monocyte leaves the blood stream and enters tissue, it transforms into a mature macrophage. Macrophages live within tissue spaces in widespread locations (Abramson and Melton, 2000). These cells have different names related to the particular tissue. Macrophages arrive in about 5 hours after injury and become the predominant within 48 hours. Macrophages lie within the tissue spaces; it is usually the first cell to engulf and process the antigen and present it to the immune cells (lymphocytes) in a manner to stimulate a specific immune response to particular antigen. In other words, the macrophage can destroy the organism while keeping its cell surface markers to give lymphocytes so that can always identify that particular organism and mount a specific defense against it (Naskalski *et al*., 2007).

Lymphocytes are nongranulocytes and responsible for immune responses to specific organisms. They are the most numerous circulating WBC after neutrophils. There are 2 major classes of lymphocyte: the T lymphocyte (T cell) and the B lymphocyte (B cell) (Entrican *et al*., 2002). Both T and B cells can be sorted into subtypes based on characteristic surface molecules on them called cluster of differentiation

(CD). Cluster of differentiation surface molecules assist in defining the function of the different lymphocyte subtypes.The T cell matures in the thymus and is responsible for cell-mediated immunity. The T cell can also stimulate the B cell, which matures in the bone marrow and is responsible for humoral, known as antibody-mediated, immunity (Park *et al*., 2004).

Behavioural parameter assessment

Behavioural changes are useful tools for the recognition and evaluation of pain and stress in animals (Broom and Johnson, 2000; Mellor *et al.*, 2005; Rushen, 2005). Behavioural assessment is probably the best and more reliable way to recognize pain in sheep, provided that the observer has a good knowledge of natural behavior of animals. Although ruminants' signs of pain are not very easy-to-read, there is some general behaviour that is usually considered significant. These are total or partial anorexia, dullness, depression, gait changes, open mouth breathing, grunting, leaning or nose pressing, teeth grinding, reduced grooming behaviour, stretching hind limbs and aggressive behaviour (Dobromylskyj *et al*., 2005; Van Reenen *etal.*, 2005).

Kicking the abdomen, rolling and posture changes are signs of abdominal pain in sheep and other animals, although never as extreme as in horses. In addition to the above parameters, feed and water intake are behavioural parameters which were included in this study. Careful examination and a good knowledge of natural behaviours are needed because most of these signs are subtle and not very specific. Some behaviours used to describe animal pain are well known and relatively easy to interpret. However, some changes are less evident and can even be puzzling. Lambs increased activity and sometimes eating after tail-docking and castration. In contrast, reduced activity is understandable after painful procedures– resting may help recovery and reduce pain recurrence due to movement (Broom and Fraser, 2007). Certain disturbed behaviours such as vocalization, head shaking, stamping, licking, scratching or rubbing and transitions have been used as indicators of pain-related distress after laparotomy and castration in sheep and cattle (Ting *et al.*, 2003a; Mellor *et al.*, 2005; Vickers *et al.*, 2005; Doherty *et al.*, 2007; Stafford, 2007).

Problems of Pain Assessment in Animals

Humans and animals have common anatomical and physiological features but that has given rise to an important question: Why is animal pain so often ignored? The first answer to this question would be that our ability to assess pain in farm animals is still very limited. However, the fact that pain is not fully recognized does not mean that it does not exist. This is particularly true for ruminants in which concealment of vulnerability and weakness appears to be adaptive (Broom, 2001a; Dobromylskyj *et al*., 2005; Weary *et al.*, 2006). Therefore, the signs of pain in these species are without a doubt, very subtle. If identifying and grading acute pain presents such difficulty, trying to evaluate the degree of long term pain is much harder, although perhaps more important for animal welfare (Stafford, 2007).

There are four common problems to explain why humans have some difficulty in recognizing pain in animals: misdescription not being able to correctly describe signs of pain in animals or using words that apply to humans but not necessarily to animals; misrepresentation humans relate certain behavioural features (crying, bellowing, complaining etc) to the ability to feel pain. The absence of evidence of these features would imply that feelings and emotions are also missing. The famous statement "I think, therefore I exist" is a common misrepresentation; misdirection physical pain is admitted but not emotional suffering. If anthropomorphic reasoning is excluded from pain assessment then suffering is not evident and misperception animals are seen as instruments with no intrinsic value (Linzey, 2006). When assessing pain, care should be taken to analyses potential conflict of interests because studies have shown that animals will endure pain if a superior interest is at stake. For example rats would tolerate some stress in exchange for food reward and lame chickens showed fewer signs of pain when put in a new cage or together with a strange animal or when being fed (Gentle, 2001). Likewise, sheep will probably reduce the signs of pain in the case of fear, which may occur in the presence of humans, other animals or aversive surroundings (Gentle, 2001; Pajor *et al.*, 2003). Another problem in assessing pain is to scale the different changes found. By daily monitoring, practitioners and farmers can usually estimate pain duration but have difficulty in estimating pain intensity (Meyer and Marrow, 2004).

Types of Pain Responses in Animals

Based on the scope of this study, it is often classified into physiological/clinical response, leukocyte response and behavioural response (Sadovsky, 2000).

Clinical/physiological response to pain

Besides measuring the activity of the physiological system, it is possible to make measurements of the activity of the heart rate, rectal temperature and respiratory rate (Molony and Kent, 1997). This includes changes in the cardiovascular system (altered heart rate, changes in pulse quality and decrease in peripheral circulation), respiratory system (abnormal breathing pattern, altered rate and depth); increasing rectal temperature is the major indicator of pain and inflammation. Increase pupillary diameter, skin resistance and blood resistance are types of physiological response. As animals in pain frequently have an elevated heart and respiratory rate and a reduced blood supply to the extremities (Morton and Griffiths, 2005). In addition to these measurable clinical signs of painrecommended, loss of body weight gain could indicate reduced food intake which caused by pain. It is also recommended checking the quality and quantity of faeces. This would help in assessing the function of the digestive system, which could also be affected by pain (Diesch *et al*., 2009; Gibson *et al*., 2009; Johnson *et al*., 2009; Goodrich and Mama, 2011; Michels *et al*., 2011).

Leukocyte response to pain

The total leukocyte and differential leukocyte count is expressed in cubic millimeters and percentages respectively. An elevation in the total leukocyte count is called leukocytosis. Leukocytosis most commonly identifies infection, tissue inflammation, surgery or tissue necrosis associated with disorders such as acute myocardial infarction, burns, gangrene, leukemia, radiation exposure, extremes in heat or cold (Cannon *et al*., 2001). The role of leukocyte in postoperative pain and inflammation is currently being studied. Postoperative patients with elevated leukocyte counts after surgical event have been found a greater risk than those with lower leukocyte counts. Leukocytosis may also occur in response to physical and emotional stressors such as overexertion, seizures, anxiety and epinephrine administration. However, stress leukocytosis will return to normal within an hour. In the preoperative setting, an elevation in the leukocyte count frequently causes postponement or cancellation of a surgical procedure for further evaluation. If the total leukocyte count is elevated, the differential and the patient should be evaluated and the surgeon and anesthesia provider notified (Sadovsky, 2000).

An evaluation of the differential leukocytes will allow for further discrimination. Neutrophilia is an increase in the total neutrophil count because neutrophil account for greater than 96% of all granulocytes, neutrophilia may also be referred to as granulocytosis. It is the most common cause of elevated leukocyte count. An elevation in segmented neutrophils is considered a “shift to the right.” An elevation in bands is referred to as a “shift tothe left,” which means that there are an increased number of immature neutrophils released from the bone marrow and circulating in the blood. Clinically, the term shift to the left specifies an acute bacterial infection has depleted the normal reserves of mature neutrophils and the bone marrow has had to resort to releasing immature ones where as a shift to the right can be considered a result of tissue damage or necrosis (Abramson and Melton, 2000).

Behavioural response to pain

The study of behavioural patterns should constitute a substantial part of pain assessment. People tried to define species-specific signs of behaviour indicating pain. These included changes in posture (anxious glances, tail between legs), vocalising (howls, distinctive bark), changes in temperament (aggression or cringing and extreme submissiveness) and other changes (penile protrusion and frequent urination and defecation) (Thornton and Waterman Pearson, 1999). There exist certain species-specific behavioural changes that can be measured and quantified. As changes in locomotor activity such as increased restlessness, kicking, stamping, rolling, jumping, easing quarters, licking or biting at the damaged site and tail wagging are indicators of pain response. Some of these behaviours are considered to have no beneficial effects; however, these can be described as attempts to escape and may be interpreted as specific pain behaviour (Molony and Kent, 1997).

This methodology was successfully used for estimation of behavioural responses to the pain of castration in calves (Molony *et al*., 1995) or tail docking in lambs (Landa, 2003). Behavioural changes can be used for the assessment of acute pain in piglets undergoing ear tagging or notching. These procedures produced pain-related behaviour like head shaking (vigorous toss of head from side to side, flapping of ears), ear scratching (rubbing against the floor or the sides of the crates), vocalisation (squeal or grunting more guttural forms of vocalisation) and finally shivering (trembling as though cold) (Leslie *et al*., 2010; Love *et al*., 2011). Scientists tried to determine changes in facial expressions during a brief painful stimulus using kinematic analysis of facial movements. This technique was successfully used for measurement of facial muscle movements and although further research is required, changes in facial expression due to pain represent a very interesting and original approach to pain assessment in animals. Examples of equid-specific behavioural indicators of pain originating from various parts of the body include deep groaning, rolling, kicking at abdomen and stretching(Ashley *et al.*, 2005).

Persistent Post-operative Pain

Pain persisting beyond 3 to 5 days after surgery is only now being recognized as a negative outcome in its own right. 32 to 50% of patients undergoing amputation, mastectomy, thoracotomy or sternotomy still show persistent pain 3-6 months after surgery, with 5-10% of these reporting severe pains (Kehlet *et al*., 2006). Even minor interventions such as inguinal herniorrhaphy are associated with significant incidences of postoperative persistent pain (Aasvang and Kehlet, 2005). Pain after surgery has a major and significant medical and societal impact. It should be noted that oncepersistent pain becomes chronic pain, a maximum of one third of the patients will benefit from presently available therapeutic options (Kehlet *et al*., 2006).

The factors contributing to persistent postoperative pain can broadly be divided between patient and surgical factors. Patient factors include pre-existing pain conditions, genetic predisposition to exaggerated pain response. Surgical factors include the type of anaesthesia administered (general verses regional technique) and surgical approach including the ability to identify and avoid nerve injury when possible. Additional surgical factors include the postoperative period and the type of pain treatment and duration and full assessments of the pain, its consequences and neurophysiological examination (Kehlet and Rathmell, 2010).

The mechanism of persistent post-operative pain is complex and poorly understood. Many of the syndromes are neuropathic that result from neuroplastic changes after injury (Macrae, 2008). After surgical intervention, patients experience ongoing pain is sensitive to incidental, normally non-painful stimulation. In uncomplicated wound healing; painprogressively attenuates and disappears. The patient population with persistent post-surgical pain experience deep pain or referred pain that lasts months or years. The International Association for the Study of Pain (1994), defined as a persistent pain state that is apparent more than two months after operation and cannot be explained by other causes. The nature and properties of this pain are poorly characterized, without a distinct transition period from acute to chronic pain (Kehlet *et al.*, 2006; Scholz and Yaksh, 2010). It is also common 1 year after lower abdominal surgery, sternotomy, hysterectomy, and herniorrhaphy with rates of 25% (Bruce *et al.*, 2004). This problem is not restricted to major surgeries; after minor procedures, approximately 5% of patients suffer severe persistent post-surgical pain (Jenkins and O'Dwyer, 2008; Kehlet *et al*., 2006; Walker *et al*., 2009).

Management of Post-operative Pain in Animals

Most of the surgical procedures can be performed safely and efficiently in ruminants using a combination of physical restraint, mild sedation and local anaesthesia. The 2% lidocaine hydrochloride has become the most commonly used local anaesthetic agents in ruminants because of low cost and limited toxicity (Edwards, 2001; Smith *et al.*, 2002; Anderson and Muir, 2005b; Doherty *et al.,* 2007; Edmonson, 2008). However, postoperative pain is managed using analgesia. Effective pain management in sheep should be combining the reduction of primary and acute pain with the prevention of secondary (central or peripheral) hypersensitivity (Nolan, 2000; Hewson *et al.*, 2007). Practitioners and veterinarians are usually more concerned with the first pain but will often neglect the control of pathologic or chronic pain. This happens because it is less obvious, its' control is more expensive and it does not pose safety problems for the operator. Acute pain in sheep practice is usually addressed by local or regional anaesthesia on the time of surgery (Huxley and Whay, 2006; Edmondson, 2008).

NSAID include a variety of different agents of different chemical classes. Most of these drugs have three major types of effect such as anti-inflammatory, analgesic and antipyretic effect. The first two are essential for pain management: anti-inflammatory effect–modification of the inflammatory reaction and analgesic effect–reduction of some types of pain (Rang *et al.*, 2003a; Fulwider *et al.*, 2008). All of these effects are related to the primary action of these drugs: cyclo-oxygenase enzymes inhibition, reducing inflammation by decreasing the production of prostaglandins, tromboxane A2 and other inflammation mediators (Lees *et al.*, 2004).

Stimuli of various muscle incisions can be start-up a cascade of processes involved in inflammation. An important step in this process is the conversion of arachidonic acid into the prostaglandin precursor PGH2 by the enzyme cyclooxygenase. COX-1, a constitutive enzyme, supports the production of physiologically relevant prostaglandins, regulating the production of cytoprotective gastric mucus, platelet aggregation, controlling renal blood flow and tissue homeostasis. Inhibition of COX-1 is responsible for the known potential side-effects such as ulceration of the upper gastrointestinal tract and delayed blood clotting. COX-2, an inducible enzyme, is responsible for the formation of pro-inflammatory prostanoids; these prostanoids are for a large part responsible for the undesirable effects of the inflammatory reaction such as pain and fever. COX-2 is induced in inflammatory cells when it activated, being responsible for inflammation activation and mediation (Vane and Botting, 2001).

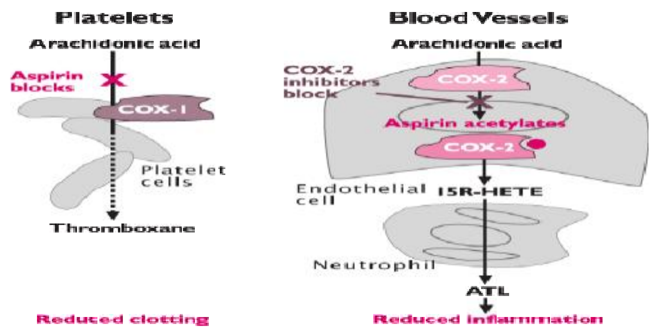

Fig. 5: Conversion of arachidonic acid into the prostaglandin precursor PGH2 by the enzyme cyclooxygenase.

NSAIDs are mainly effective against pain associated with inflammation or tissue damage because NSAID decrease production of mediators (PGE2 and PGI2) that sensitize peripheral nociceptors terminals producing localized pain and also hypersensitivity (Stock *et al.*, 2001; Rang *et al.*, 2003a). NSAID also reduce other components of the inflammatory and immune response that cause pain, namely vasodilatation and oedema. However, some NSAID showed analgesic effects other than those due to inflammation reduction (Rang *et al*, 2003a; Bunsberg, 2008). These drugs show activity at nervous central level (spinal nociception and central sensitization) by inhibiting COX-2 activated PGE2 that lowers the threshold for neuronal depolarization and increases the number of action potentials and repetitive spiking (Watts and Clarke, 2000; Huxley and Whay, 2006; Hewson *et al.*, 2007; Huxley *et al.*, 2008).

Efficacies of some NSAIDs are comparable to opoids in many cases of surgical, musculoskeletal and visceral pain (Nolan, 2000; Bunsberg, 2008). The pre-emptive use of NSAID shows some drawbacks in severely ill, dehydrated or general anaesthetized animals because of inhibition of prostaglandins that are necessary for adequate renal function. NSAIDs are used in farm animals mostly for anti-inflammatory and anti-toxic activity. NSAIDs have been shown to be effective in controlling pain in many clinical situations such as postsurgical pain, arthritis, colic, and traumatic lesions (Hewson *et al.*, 2007). Meloxicam has been reported as a safe substitute of diclofenac sodium (Green *et al.*, 2007).

Meloxicam is a NSAID derived from oxicam. Meloxicam acts by inhibition of prostaglandin synthesis exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects. It reduces leukocyte infiltration into the inflamed tissue. Meloxicam is chemically designated as 4-hydroxy-2-methyl- N -(5-methyl-2-thiazalyl)-2 H -1,2-benzothiazine-3-carboxamide-1,1-dioxide and belongs to oxicam class of NSAIDs. It has molecular formula $C_{14}H_{13}N_3O_4S_2$ and the molecular weight of 351.4 Dalton. It preferentially inhibits cyclooxygenase-2 which is responsible for pathophysiological conditions rather than cyclooxygenase-1 responsible for physiological processes (Churchill *et al.*, 1996).

Treatment with meloxicam reduces local swelling, inflammation and pain by inhibiting cyclooxygenase enzyme, which is the rate-limiting enzymatic activity in the conversion of arachidonic acid to pro-inflammatory prostaglandins. Meloxicam is used in humans, horses, dogs and other farm animals for the relief of inflammation and pain in both acute and chronic musculo-skeletal disorders. In horses, meloxicam is also used for the relief of pain associated with colic. In general, meloxicam is also used to reduce post-operative pain and inflammation following orthopaedic and soft tissue surgery. The indication in cats is reduction of post-operative pain after a spay operation and minor soft tissue surgery. A dose of 0.5 mg/kg meloxicam is administered to animals as clinically effective as up to 3 consecutive days through intramuscular route (Sinclair *et al*., 2006). Meloxicam reduced heat, protein, lactic dehydrogenase, leukocyte numbers, PGE2, and thromboxane A2 in exudates obtained from the site of inflammation. This effect was greatest at 8 hours of administration. Meloxicam levels gradually increased over time at the inflamed site. Only a slight temporary swelling at the injection site following subcutaneous administration was observed in less than 10 % of the cattle treated in clinical studies. It has a half-life of 20-24 hours in animals and once-daily administration is considered appropriate for 24 hours. It is strongly bound to plasma proteins (99.5%) compared to other NSAIDs (Davies and Skjodt, 1999).

Most of meloxicam is eliminated after biotransformation. The metabolites of meloxicam do not alter the renal blood flow and consequently the drug is not capable for nephrotoxicity. The therapeutic index of meloxicam is higher when compared with other NSAIDs like piroxicam, diclofenac and indomethacin (Englhardt *et al*., 1995). All NSAIDs have been shown to have almost similar efficacy. But, meloxicam shown to be superior as far as GIT tolerability was concerned. It was probably due to preferential and selective inhibition of cyclo-oxyginase-2 as compare to cyclo-oxygenase-1. Its gastrointestinal tolerability was superior to that of nonselective NSAIDs (Schofield and Williams, 2004).

Conclusion and Recommendations

Meloxicam is pain killer in sheep and other farm animals post-operatively. Collectively, different studies indicated that meloxicam had improved the quantitative measures including feed intake. It had arrested abnormal increase of rectal temperature, heart rate, respiratory rate, total and differential leukocyte count post-operatively. In addition to relief of pain, it is important to improve the welfare of animals because freedom from pain and disease are one of the five freedoms of animal welfare. Based on the above conclusions, the following recommendations are forwarded: post-operative administration of meloxicam should be practiced in all types of surgery in sheep to maintain physiological, hematological and behavioural parameters; awareness should be created among veterinarians to practice administration of meloxicam a NSAID in management of pain and sever inflammation in sheep and adequate guidelines for postoperative pain management should be distributed to improve the welfare of millions of sheep.

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