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Comparison of the Efficacies of Meloxicam and Flunixin Meglumine on some Haemostatic Variables in Dehorned Holstein Heifers

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Summary: Dehorning may cause physiologic, behavioral and neuroendocrine alterations accompanied by a stressful/ painful response among cattle. Non-steroidal anti-inflammatory drugs mitigate the pain response related to dehorning; however, their efficacy on hemostasis is not well-known. Moreover, the haemostatic profile of cattle has to be taken into consideration prior to surgery in order to prevent alterations or dysfunction in coagulation. This study was conducted to evaluate the efficacy of meloxicam and flunixin meglumine administration on the coagulation profiles of Holstein heifers subjected to dehorning. Heifers (n=14) were administered either meloxicam (0.5 mg/kg, i.v.) or flunixin meglumine (2.2 mg/kg, i.v.) in a single dose prior to dehorning. Fibrinogen (F), prothrombin time (PT), and activated partial thromboplastin time (APTT) were determined prior to dehorning (time 0) and 90 minutes after administration. Fibrinogen concentration (mean ± SEM) in the heifers that received meloxicam was significantly increased (P<0.05) 90 minutes after administration (238.83±14.22 mg/dL) in contrast to initial values (212.86±8.13 mg/dL). Significant differences were not detected in other coagulation panel parameters at sampling times. Intravenous administration of single dose meloxicam or flunixin meglumine was determined not to cause significant changes of selected haemostatic variables in heifers subjected to dehorning.

Key words: Cattle, dehorning, flunixin meglumine, hemostatic function, meloxicam

Boynuzsuzlaştırılan Holstein Düvelerde bazı Hemostatik Değişkenler Üzerine Meloksikam ve Flunixin Meglumin Etkinliğinin Karşılaştırılması

Özet: Boynuz köreltme sığırlar için stresli/ağrılı tepki eşliğinde fizyolojik, davranışsal ve nöroendokrin değişikliklere neden olur. Non-steroid anti-inflamatuar ilaçlar boynuz ile bağlantılı ağrı tepkisini azaltır; Ancak, hemostaz üzerindeki etkinlikleri iyi bilinmemektedir. Ayrıca, sığır hemostatik profili pıhtılaşma değişiklikleri veya işlev bozukluğunu önlemek amacıyla ameliyat öncesi göz önüne alınmalıdır. Bu çalışmada, boynuzsuzlaştırma yapılan Holstein düvelerde meloksikam ve fluniksin meglumin uygulamasının pıhtılaşma profillerine etkinliğini değerlendirmek amacıyla yapılmıştır. Düvelere (n=14) boynuzsuzlaştırma öncesi meloksikam (0.5 mg/kg, i.v.) veya fluniksin meglumin (2.2 mg/kg, i.v.) tek doz halinde uygulandı. Fibrinojen (F), protrombin zamanı (PT) ve aktive edilmiş kısmi tromboplastin zamanı (APTT) boynuzsuzlaştırmadan önce (0. dakika) ve boynuzsuzlaştırma sonrası 90 dakika olarak belirlendi. Meloksikam uygulanan düvelerde fibrinojen konsantrasyonu (ortalama ± SEM) başlangıç değerlerinin (212.86±8.13 mg/dl) aksine 90 dakika sonra (238.83±14,22 mg/dL) anlamlı artış gösterdi (P<0.05). Diğer pıhtılaşma parametrelerinde önemli bir değişiklik tespit edilmedi. Boynuz kesimi uygulanan düvelerde meloksikam ve fluniksin meglumin'in tek doz intravenöz uygulamalarının seçilen hemostatik değişkenlerde önemli değişikliklere neden olmadığı gözlendi.

Anahtar kelimeler: Boynuzsuzlaştırma, flunixin meglumine, hemostatik fonksiyon, meloxicam, sığır

Introduction

Dehorning (DH) used in older cattle with grown horns, is a common and painful, yet important procedure in both dairy and beef industries (19,22,28). Regardless of the method used, postoperative pain can continue for 24 to 44 h (3,10,26).

Dehorning of calves is also a common procedure in Turkish commercial dairy farms. Pain management of calves subjected to dehorning has been thoroughly investigated in various studies (2,3). Local anesthetic administration prior to dehorning is essential for pain relief. Non-steroidal anti-inflammatory drug (NSAID) should be used to reduce post-operative pain (13).

Meloxicam and/or flunixin meglumine are commonly used as analgesics in cattle practice in Turkey for relieving the pain due to dehorning but the effects of these drugs after a single i.v. administration on the hemostatic profile of heifers subjected to dehorning with local anesthesia

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have not been well investigated. The authors were unaware of any reports regarding the effects of meloxicam or flunixin meglumine on the coagulation cascade during the pre- or perioperative period. This study was aimed to evaluate the efficacy of single dose meloxicam and flunixin meglumine administration on some haemostatic variables of Holstein heifers subjected to dehorning.

Materials and Methods

Animals and dehorning procedure

A total of 14 healthy heifers, 9 to 12 months old, from a commercial dairy farm were used in this study. The heifers were randomly (by coin toss) assigned to two groups: group meloxicam

(Group mlx, n = 7), and group flunixin meglumine (Group flnx, n=7). The study followed the University's procedures for animal research (Adnan Menderes University Ethics Committee, 3/2015).

The basis of both horns were shaved and the area cleaned with iodine solution. Heifers were sedated with i.v. 0.05 mg/kg xylazine, and both cornual nerves were blockaded with SC 10 mL of 2% lidocaine SC (31). Ten minutes prior to dehorning 0.5 mg/kg of meloxicam (Bavet Meloxicam® BAVET, Istanbul, TR) were administered to Group mlx, and 2.2 mg/kg of flunixin meglumine (Fundamin® BAVET, Istanbul, TR) were administered to Group flnx through the jugular vein. Horns were amputated 15 min after cornual nerve blockade using a Barnes dehorner and haemostasis was maintained with thermal cauterization (28).

Blood sampling and laboratory analysis

Blood samples in all heifers were collected prior to sedation and administration of local anesthesia and 90 min after dehorning. Four mL of blood were withdrawn via the jugular vein into a polypropylene tube dressed with 0.1 mL of sodium citrate and analyzed for some haemostatic variables: activated partial thromboplastin time (APTT, seconds), prothrombin time (PT, seconds), and fibrinogen (F, mg/dL) using a microcoagulator (Beijing Precii Instrument Co. Ltd. C2000-4 semi-automatic blood coagulation analyzer, Guanzgzhou).

Statistical Analysis

Descriptive statistics were obtained for the coagulation variables. Because the variables were normally distributed, the parametric Paired Sample T test was used and the statistical results were checked with non-parametric Wilcoxon test (SPSS ver. 15.0 for Windows - SPSS Inc., Chicago USA). Statistically significant differences were set at $P < 0.05$.

Results

Mean and range values for the variables measured are shown in Table 1. The administration of meloxicam or flunixin meglumine did not have any effect on PT or APTT. However, F concentration was increased (P = 0.051) significantly 90 min after dehorning in group mlx (238.8 vs 212.9 mg/dL at time 0) compared to group flnx (Table 1).

Table 1. Hemostatic tests in Holstein heifers subjected to dehorning and administered meloxicam (Group mlx) or flunixin meglumine (Group flnx).

Variable	Group	Time[1]	Mean ± SEM	Range	P values
PT (sec)	Mlx	0	20.57 ± 0.57	18.10 – 22.40	0.419
		90	21.29 ± 0.37	20.30 – 23.10	
	Flnx	0	19.80 ± 0.34	18.60 – 21.10	0.573
		90	19.46 ± 0.46	18.10 – 21.10	
APTT (sec)	Mlx	0	26.84 ± 0.85	24.60 – 30.50	0.705
		90	27.23 ± 1.08	24.60 – 32.60	
	Flnx	0	25.77 ± 1.31	21.20 – 31.80	0.600
		90	26.16 ± 1.55	20.00 – 33.30	
F (mg/dl)	Mlx	0	**212.86 ± 8.13**	184.60 – 242.50	**0.051**
		90	**238.83 ± 14.22**	209.80 - 321.80	
	Flnx	0	260.13 ± 35.22	196.40 – 447.10	0.742
		90	264.20 ± 28.45	201.60 – 392.90	

[1]Time 0 = blood sample taken prior to dehorning. Time 90 = blood sample taken 90 min after dehorning; SEM =standard error of the mean;
PT= prothrombin time; APTT = activated partial thromboplastin time; F = fibrinogen

Discussion

Non-steroidal anti-inflammatory drugs are commonly used in domestic animals to alleviate several inflammatory conditions including musculoskeletal disorders, soft tissue injuries, mastitis, pneumonia and postoperative pain. These compounds possess antipyretic, anti-inflammatory and analgesic properties. Their reported mechanism of action is a blockade of prostaglandin (PG) biosynthesis through the inhibition of cyclooxygenase (COX) (6,15,17). COX is the enzyme responsible for the metabolism of arachidonate and catalyzes the biosynthesis of PG (1,29).

Meloxicam belongs to the enolic acid class of NSAIDs and is available in an injectable formulation approved in the USA, the EU and Turkey for intravenous and subcutaneous administration in animals. The N-methylglucamine salt of [2 (2-methyl-3-trifluoromethylamino) nicotinic acid], known as flunixine meglumine, has proven anti-inflammatory, anti-endotoxic and analgesic properties. It also inhibits COX and decreases production of PG and thromboxane (14,16). The studies (11,12) have considered the effects of meloxicam on behavior, pain sensitivity and post-surgical stress in dairy calves following dehorning by cauterization. Coetzee et al. (2) investigated the pharmacokinetics of intravenous meloxicam in weaned Holstein calves after scoop dehorning. However, none of these studies determined its efficacy on hemostatic functions.

It has been reported that fibrinogen levels peak one to two days after tissue injury (probably due to adrenal and extra-adrenal pathways), remain high for up to 6 days, then slowly decline until reaching normal basal values, 8 to 9 days after the initial injury (7). This may be briefly explained. Taking into account that epinephrine partially involves within the plasma flbrinogen increase in rats with tissue injury (18,23,24,25), bradykinin and histamine participate in causing pain, wheraeas PG decrease the pain threshold (4,5), a pathway including sensitive nerve endings-central nervous/sympathetic systems-adrenal medulla, all proposed somewhat constrained for the plasma fibrinogen elevation determined in rats laparotomized (7). It was also hypothesized that some products derived from the interaction of PGE 1, bradykinin and/or histamine might be involved in plasma fibrinogen increase in injured rats. Contrarily in medullectomized animals injected with PGE 1+histamine or bradykinine+histamine, significant decrease of plasma fibrinogen levels was also observed. According to the aformentioned alterations the researchers suggested that those drugs partly act through the adrenal medulla (8). In the present study fibrinogen levels were measured on 0. and 90th minutes thereafter meloxicam or flunixin meglumine administration. It may be speculated that tissue injury and related alterations (23,24,25) or meloxicam, might act through the adrenal medulla resulting with fibrinogen increases on 90th minutes.

In the case of multiple injuries, such as dehorning, fibrinogen values remain elevated because the inflammatory response stimulates the liver to synthesize and release acute-phase reactants, as well as fibrinogen (9). It is known that F might cause and contributes to the progression of ischemic disease (27). Moya et al. (20) investigated the pharmacological effects of meloxicam on rats subjected to multiple injuries, and found that fibrinogen levels significantly increased in the latter group. Afterwards meloxicam administration resulted with a decrease in fibrinogen values in relation to inhibition of COX in multiple injured animals. It has been well recognized that COX plays a role within the conversion of the arachidonic acid into PG. Hence meloxicam is responsible for the preferential inhibition of COX, it also causes reduction of PG biosynthesis. Furthermore, PGE2 is mediating the synthesis and secretion of fibrinogen, meant that a decline in PG synthesis would also decrease fibrinogen concentration (20). Moreover, it was also suggested that mix might also block cytokine release involved within the inflammatory process, in which fibrinogen uses this route for elevating its production (5).

Circulating fibrinogen levels was not significantly altered by meloxicam administration in beef steers following long-distance transportation (30). Fibrinogen coordinates homeostasis via supplying fibrin formation and tissue repair (21). Although it is not clear whether an elevated plasma fibrinogen level on 90. min itself increases in mix group, and on contrarily reports aforementioned above indicating meloxicam administration causing decrease in fibrinogen values (20), it may be speculated that fibrinogen might cause and contributes to the progression of ischemic disease (27) or tissue repair (21). Furthermore, the present authors may speculate

that meloxicam may have helped decreasing the severity of elevation for fibrinogen values in treated cattle. It may also be suggested that hyperfibrinogenemia probably persists longer (20), even if meloxicam was not administered in the present cases.

In conclusion, intravenous administration of meloxicam or flunixin meglumine at a single dose in heifers subjected to dehorning causes slight changes in selected haemostatic variables. Meloxicam only caused elevations on fibrinogen (at 90th min) concentration. Although only a limited number of cattle were involved, when meloxicam is used in cattle before surgery for its analgesic effect, it should cause significant alterations on the hemostatic properties during the dehorning operation.

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