Atatürk Üniversitesi Vet. Bil. Derg.
2016; 11(2): 146-150

Research Article/Araştırma Makalesi
DOI:10.17094/avbd.34295

Atatürk Üniversitesi Veteriner Bilimleri Dergisi

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Evaluation of the Effect of Ketoprofen on Haemostatic Parameters in Holstein Heifers Following Dehorning

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Geliş Tarihi/Received	Kabul Tarihi/Accepted	Yayın Tarihi/Published
25.05.2016	13.07.2016	31.10.2016

Abstract: Ketoprofen (KTP), an aryl propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) with the potential of a strong non-selective inhibition of cyclooxygenase (COX). KTP mitigates dehorning pain in cattle. The coagulation status of the cattle has to be taken in to consideration prior to surgery in an attempt to prevent haemostatic alterations or dysfunction. In this study, the effect of administration of KTP on the coagulation profiles of Holstein heifers subjected to dehorning is evaluated. Heifers (n=7) were treated with KTP (2.2 mg/kg i.v.) for a single dose prior to dehorning. Fibrinogen (Fb), prothrombin time (PT), activated partial thromboplastin time (APTT) were determined prior to administration (0.) and 30, 60 and 90 minutes later. Taking into account the mean values (±SD) obtained, the PT was significantly increased on 30. minutes in contrast to initial values ($P<0.05$). Similarly, Fb concentration showed statistical significance on 60. minutes ($P<0.05$) in comparison to the initial values. Significant differences were not detected in other coagulation panel parameters at sampling times. In conclusion, i.v. administration of KTP at a single dose in heifers subjected to dehorning causes slight changes of selected haemostatic variables. KTP only caused elevations on PTT and Fb. Based on these results, when KTP is used in cattle before surgery for its analgesic effect, it should cause alterations on the haemostatic properties during the dehorning.

Keywords: Cattle, Dehorning, Haemostatic function, Ketoprofen.

Holstein Düvelerde Boynuzsuzlaştırmayı Takiben Ketoprofenin Hemostatik Parametrelere Etkisinin Değerlendirilmesi

Öz: Aril propiyonik asit türevi olan Ketoprofen (KTP) seçici olmayan güçlü bir siklooksijenaz (COX) inhibisyonu ile nonsteroidal anti-inflammatuar ilaçlar arasındadır. KTP sığırlarda boynuzsuzlaştırma ağrısını hafifletir. Sığırların pıhtılaşma özellikleri hemostatik değişiklikler veya fonksiyon bozukluklarını önlemek amacıyla ameliyat öncesi dikkate alınmalıdır. Bu çalışmada boynuzsuzlaştırma işlemi uygulanan düvelerde KTP'nin koagülasyon profillerine olan etkisi değerlendirildi. Düvelere (n=7) boynuzsuzlaştırma öncesi KTP (2.2 mg/kg i.v.) tek doz uygulandı. Fibrinojen (F), protrombin zamanı (PT) ve active edilmiş parsiyel tromboplastin zamanı (APTT) uygulama öncesi (0.), 30., 60. ve 90 dakikalarda belirlendi. Ortalama değerler (±SD) dikkate alındığında, PT değerleri başlangıç değerlerinin aksine 30. dakikada belirgin bir artış oldu ($P<0.05$). Benzer şekilde Fb konsantrasyonu başlangıç değerlerine göre 60. dakikada istatistiksel olarak anlamlı ($P<0.05$) görüldü. Örnekleme zamanlarında diğer koagülasyon parametrelerinde önemli farklılıklar tespit edilmedi. Sonuç olarak, boynuzsuzlaştırma işlemi uygulanan düvelere tek doz KTP'nin iv uygulanması seçilen hemostatik değişkenlerde hafif değişimlere neden oldu. KTP sadece PTT ve Fb'de artışlara neden oldu. Elde edilen sonuçlara göre sığırlarda analjezik etkilerinden dolayı cerrahi mühalale öncesi KTP kullanıldığında hemostatik özellikler üzerine etkileri olduğu söylenebilir.

Anahtar Kelimeler: Sığır, Boynuzsuzlaştırma, Hemostatik fonksiyon, Ketoprofen.

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INTRODUCTION

Dehorning is a frequently used application involving dairy calves. Indeed, less than 20% of producers report using analgesics and/or anaesthetics during the procedure (1,2). Contrarily, analgesic drugs may be of beneficial at the time of dehorning. Hence, cornual nerve blocks takes place in 10–15 minutes, providing pain relief for a limited duration (3). On the other side, if the coagulation cascade of the cattle remains unclear prior to surgery, haemostatic alterations may occur (4). Given the common usage of KTP as an analgesic in cattle practice for relieving pain due to dehorning (5,6), the primary objective of this trial was to describe the effects of KTP after a single i.v. administration on selected haemostatic profile in heifers subjected to dehorning with local anaesthesia. The present authors were unaware of finding documented reports regarding the effects of KTP on coagulation cascade during pre or perioperative period.

MATERIALS and METHODS

Dehorning Procedure

A total of 7 Holstein heifers, aged between 9 to 12 months, from a commercial dairy farm were enrolled in this study. This study was conducted in accordance with the university guidelines for animal research (Adnan Menderes University Ethics Committee, 3/2015).

Calves were dehorned by using Barnes dehorner. Hairs around the base of the both horns were shaved and cleaned. Heifers were injected with 0.05 mg/kg Xylasine IV, and 10 mL of 2% lidocaine SC, to block the cornual nerve (7). Into jugular vein, 3 mg/kg KTP were administered 10 minutes prior to dehorning procedure. After 15 minutes of the cornual nerve block, amputations of the horns were performed via Barnes dehorner. Bleeding was controlled with thermal cauterization (8).

Coagulation Tests

Blood samples were collected from 7 Holstein heifers at the beginning of the trial (that meant prior to administration of sedation and local anaesthesia) and again at 30^{th}, 60^{th} and 90^{th} minutes after dehorning procedure. A total of 4 ml of blood was collected by venepuncture from the jugular vein into a polypropylene tube containing 0.1 ml of sodium citrate for a coagulation panel including prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen (Fb). Coagulation panel involving PT (seconds), APTT (seconds) and Fb (mg/dl) concentrations were analysed by use of a microcoagulator (Beijing Precii Instrument Co. Ltd. C2000-4 semi-automatic blood coagulation analyser, Guanzgzhou).

Statistical Analysis

The measurements for the above coagulation parameters were tabulated above the descriptive statistics. Mean, standard deviation, maximal and minimal values were shown. The parameters were not normally distributed after the normality tests and logarithmic transmissions. Then statistical analyses were done with non-parametric Wilcoxon test and statistical significant differences were set at $P < 0.05$. Software package (SPSS ver. 17.0 for Windows - SPSS Inc., Chicago USA) were used for all tests.

RESULTS

In heifers subjected to dehorning, which were receiving KTP, the PT was significantly increased at 30^{th} minute in contrast to initial values at 0^{th} minute ($P<0.05$). Similarly, Fb concentration showed statistical significance at 60^{th} minute ($P<0.05$) in comparison to the baseline values (Table 1). Significant differences were not detected in other coagulation panel parameters at sampling times.

Table 1. Values of blood coagulation tests in Holstein heifers subjected to dehorning.
Tablo 1. Boynuzsuzlaştırma yapılan Holstein düvelerde kan koagülasyon testlerinin değerleri.

Variable	Time	Mean±Std. Er.	Range	P Value
PT	0 th minute	20.94±0.685	20.00-22.20	
	30 th minute	20.15±1.184	18.90-22.00	0.044
	60 th minute	22.08±1.595	20.20-24.50	0.176
	90 th minute	20.92±0.981	19.40-21.90	0.976
APTT	0 th minute	25.58±3.534	19.70-30.40	
	30 th minute	25.34±3.772	18.50-29.50	0.461
	60 th minute	26.72±2.359	22.50-29.10	0.214
	90 th minute	26.42±2.428	23,40-30.10	0.438
Fb	0 th minute	258.49±106.911	95.27-402.70	
	30 th minute	213.49±121.951	68.98-413.00	0.072
	60 th minute	201.65±66.933	92.86-286.90	0.036
	90 th minute	217.08±120.152	58.27-435.20	0.260

DISCUSSION and CONCLUSION

Horn buds of dairy calves are normally disbudded in an attempt to prevent injury risk to other animals or producers by use of several manipulation. It has been postulated that physiological (9,10) and behavioural studies (9,11,12) showed the evidence of pain for at least 2 h following dehorning, regardless of the method used. Prior studies evidenced that local anaesthetics administration reduced pain in the 2 to 4 h following dehorning (6-16).

KTP, an aryl propionic acid derivative, belonging to NSAID group has anti-inflammatory, analgesic and antipyretic properties (17). On the other side the latter compound has the ability to non-selectively inhibit COX, similar to other NSAIDs (18). Production of thromboxanes is necessary for primary haemostasis (19,20), however NSAID administration inhibits irreversibly the COX activity (21), resulting with haemorrhage risk (20). In cattle practice KTP is widely used in an attempt to mitigate dehorning pain (5,6). In addition, it has emerged as an alternative therapeutic option for therapy of painful conditions in bovine species. KTP is given by intravenously and parenteral routes in cattle and its usage should be limited to five consecutive days at most to reduce the risk of gastrointestinal effects (22). Side effects like haematological alterations and other relevant ones have been reported (23-27). However, the data on safety of repeated administration of KTP in cattle are lacking. Given its frequent usage, data on the effects of KTP administration with local anaesthesia on coagulation cascade in cattle subjected to dehorning are lacking. The latter reason motivated us to plan, perform and analyse the present study.

In a prior study KTP given in addition to a sedative and local anaesthetic and administered, before and after hot iron dehorning of calves reduced pain following dehorning (5). Another trial with a total of a 20 dairy calves experimentally dehorned (heat cauterization), KTP, in addition to local anaesthesia with lidocaine, reduced pain following dehorning (28). None of those studies evaluated coagulation cascade prior to and after KTP administration. In the present study, after KTP administration PT and Fb concentration were significantly increased ($P<0.05$) at 30^{th} and 60^{th} minutes, respectively. However, no other significant differences were not detected in other coagulation panel parameters at sampling times. Therefore, we may recommend KTP for preoperative use for analgesic effects, in dehorning procedure in cattle without evidence of increased bleeding.

Impairment of coagulation in cattle following administration of a NSAID might be induced by several factors involving wrong technique of taking

and processing samples (29). Blood samples were withdrawn from the jugular vein by use of commercial test tubes filled with a well-known volume of citrate. In all 7 heifers, tubes were filled with 4 ml amount of blood in an attempt to avoid misinterpretation of laboratory analysis. All samples were immediately and subsequently processed to the laboratory. Errors regarding preanalytic and analytic phases resulting with a probable abnormality thus may be ruled out, as reported previously (30).

In conclusion, intravenous administration of KTP at a single dose in heifers subjected to dehorning caused slight changes of selected haemostatic variables. KTP only caused elevations on PTT (at 30th minute) and Fb (at 60th minute). Based on these results, when KTP is used in cattle before surgery for its analgesic effect, it should cause significant alterations on the haemostatic properties during the dehorning operation.

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