Relationship among some colostral immune parameters and hepcidin in neonatal calves

Neonatal buzağılarda kolostral bazı immun parametreler ile hepsidinin ilişkisi

Research Article

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ABSTRACT

This study was designed to determine levels of hepcidin, IgG, Lactoferrin, IL-6 and iron in blood serum, colostrum, milk of healthy cows and healthy calves on different days of the neonatal period. The study included 20 pregnant cows and 20 calves born to them. Blood samples were taken from pregnant animals 15 days before the birth and immediately after the birth. Blood samples were also obtained from the calves at birth before colostrum intake and 1, 3, 7, 14 and 28 days after birth. Colostrum samples were collected from mothers immediately after birth (first milking after parturition) and milk samples were taken postpartum on days 1, 3 and 7. Concentrations of serum and colostral hepcidin, lactoferrin, IL-6 and iron were measured using commercial kits. Serum hepcidin levels of cows given birth were higher than that of pregnancy period (P>0.05). Hepcidin levels in colostrum were significantly higher (P<0.05) when compared with milk samples. Following the intake of colostrum, serum hepcidin level of calves of day 1 was similar to that of day 3 (P>0.05) and significantly higher than the values of day 7, 14 and 28 days of life in calves (P<0.001). Serum hepcidin levels had similar pattern of changes to those of IgG, Lf and IL-6 after colostrum intake in calves.
In conclusion, the results suggested that hepcidin might be an important parameter in terms of calf health, given that it had similar pattern of changes as the immune parameters studied.

Keywords: Hepcidin, immune parameters, neonatal calves

ÖZET

Sunulan çalışmada sağlıklı neonatal buzağıların kan serumu ile sağlıklı ineklerin kan serum, kolostrum ve sütündeki hepsidin, IgG, Laktoferrin, IL-6 ve demir düzeyinin belirlenmesi amaçlandı. Çalışma materyalini, 20 adet Simental ırkı gebe inek ile bu ineklerden doğan buzağılar oluşturdu. Ölçümler için gebe hayvanlardan doğumdan 15 gün önce ve doğumdan hemen sonra kan alınırken, doğan buzağılardan kolostrum almadan önce (0. saat) ve yaşamlarının 1, 3, 7, 14 ve 28. günlerinde kan alındı. Ayrıca doğumdan hemen sonra (doğum sonrası ilk sağım) annelerden kolostrum, doğumu takip eden 1, 3 ve 7. günlerde ise süt örnekleri alındı. Doğumdan hemen sonra serum hepsidin seviyesinin gebelere göre daha yüksek olduğu kaydedildi (P>0,05). Kolostrumdaki hepsidin seviyesi, süt örneklerine göre yüksek bulundu (P<0,05). Buzağıların kolostrum alımını takip eden 1 ve 3. gün hepsidin seviyesinin benzerlik gösterdiği (P>0,05) 7, 14 ve 28. günlerde 1. gün seviyesine göre önemli düzeyde düşük olduğu tespit edildi (P<0,001). Kolostrumdaki hepsidin, IgG, Laktoferrin, demir ve IL-6 seviyelerinin süte geçiş dönemine göre yüksek seviyede bulunduğu, buzağılarda kolostrum absorbsiyonu sonrasında hepsidin, IgG, Lf ve IL-6 düzeyi ile benzer şekilde değişiklikler gösterdiği belirlendi.
Sonuç olarak; hepsidinin belirtilen immun parametreler ile benzer değişiklikler göstermesi göz önüne alındığında buzağı sağlığı açısından önemli bir komponent olabileceği kanaatine varıldı.

Anahtar Kelimeler: Hepsidin, immun parametreler, neonatal buzağılar

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INTRODUCTION

Neonatal morbidity and mortality, arising from various reasons, cause significant economic losses (Erdoğan et al., 2009). The primary tool used to reduce and prevent such losses is colostrum and the passive immunity transferred by colostrum. Colostrum is composed of antimicrobial factors, nutrients, growth factors, and hormones (Pakkanen and Aalto, 1997; Godson et al., 2003; Godden, 2008). Calves are born agammaglobulinaemic (Dewell et al., 2006). Colostrum plays a significant role in the development of passive immunity through mainly immunoglobulins. Calves with serum IgG levels below 10 mg/L are diagnosed as passive transfer deficiency (Godson et al., 2003). On the other hand, studies have shown that, neonatal animals with sufficient IgG levels could be exposed to disease, animals with insufficient IgG levels may resistance to disease (Gilbert et al., 1988; Tyler et al., 1999), and this has been attributed to passive immunity components other than IgG, including growth factors, cytokines, acute-phase proteins, lactoferrin (Lf), and unidentified other factors (Barton et al., 2006; Orro et al., 2008; Gökçe et al. 2014).

Hepcidin is a low-molecular-weight antimicrobial peptide hormone. It is produced by the hepatocytes of the liver, in response to high iron (Fe) levels and inflammatory stimuli (Singh et al., 2011; Ganz and Nemeth, 2012). Furthermore, hepcidin has also been identified as a type II acute-phase protein (Singh et al., 2011). A significant relationship between hepcidin, inflammation, immunity and Fe metabolism has been reported. Hepcidin synthesis increases during infection and inflammation, through stimulation of interleukin-6 (IL-6) (Ganz and Nemeth, 2012). Hepcidin reduces the release of Fe from macrophages and duodenal enterocytes into the plasma (Anderson et al., 2007). During the course of bacterial infections, Fe is retained in tissues and cells, which reduces plasma Fe levels. This defence system is composed of Fe-binding compounds such as transferrin, Lf and ovotransferrin (Ong et al., 2006), and hepcidin the main regulator of Fe metabolism (Ganz, 2003). Hepcidin interacts with ferroportin (FPN) enabling the intermembrane transport of Fe (Nemeth et al., 2004). Following the binding of hepcidin to FPN, the hepcidin-ferroportin complex is broken down in lysosomes and Fe is trapped inside cells (mainly inside hepatocytes, macrophages and enterocytes) (Vyoral and Petrak, 2005). Therefore, both Fe and hepcidin are of great significance for immunity (Singh et al., 2011).

This study was designed to determine hepcidin, IgG, Lf, IL-6 and Fe levels in blood serum, colostrum, milk of healthy cows and the healthy calves on different days of the neonatal period.

MATERIALS AND METHODS

Animal material

The study included 20 pregnant Simmental cows and calves born from these cows. All animals were subjected to same management and nutritional conditions throughout the study period. Following parturition, the calves were weighed and bottle-fed with colostrum. An amount of 6% of body weight was given within the first 2 h. It was ensured that the calves were bottle-fed with a total amount of colostrum equalling to 10% of their body weight, within the first 12 h after birth.

Ethical Approval

This research has been approved by Kafkas University Animal Experiments Local Ethics Committee (KAU-HADYEK/2014-002).

Collection of blood, colostrum and milk samples

Blood samples were collected from the cows 15 days prior to parturition and shortly after parturition, and from the calves before colostrum feeding (day 0) and on days 1, 3, 7, 14 and 28. Blood samples were taken from the jugular vein into vacuumed gel-coated tubes (BD Vacutainer®, BD, UK). The blood samples were centrifuged at 3000 rpm for 10 min and were stored at -20°C, until being analysed.

Colostrum and milk samples were collected into tubes on day 0 (first milking after parturition) and days 1, 3 and 7 of postpartum. The samples were centrifuged at 4000 rpm for 30 min, and the lipid portion was discarded. The supernatant was stored at -20°C until being analysed.

Hepcidin, IgG, Lf and Fe measurements

Serum, colostrum and milk IgG (Bethyl®, USA), Lf (Bethyl®, USA) and hepcidin (MyBioSource®, USA) were measured using commercial ELISA kits. Fe levels were determined using an automatic biochemistry device (MINDRAY BS120®, Mindray, PRC).

Statistical analysis

Data was analysed using statistical software package SPSS® (SPSS 20, USA). The comparison of two parameters was made using t test. One-way analysis of variance (ANOVA) was used to determine changes in parameters over time. The results obtained were expressed as mean and standard error (X±SE). Values of P<0.05 and below were considered statistically significant.

RESULTS

Alterations in parameters in pregnant cows

It was determined that significant differences existed between the IgG and Lf levels measured in cows before parturition (day -15) and on the day of parturition (day 0). Serum IgG levels were determined to decrease from 1793±64.59 mg/dL to 1345±60.29 mg/dL (P<0.001), while serum Lf levels increased from 191.9±25.85 ng/mL to 337.6±42.27 ng/mL (P<0.05). On the other hand, no statistically significant alteration was determined in serum hepcidin, Fe and IL-6 levels (Table 1).

Alterations in colostral parameters

It was determined that the colostral hepcidin, IgG, Lf, Fe and IL-6 levels significantly decreased during the conversion of colostrum into milk. The values were higher in colostrum when compared to the values in milk (Table 2).

Alterations of parameters in calves

Serum hepcidin levels in calves after the absorption of colostrum on days 1 and 3 were significantly higher than the levels measured 0 h. Similarly, serum IgG, Lf and IL-6 levels were significantly increased after colostrum absorption. Serum Fe levels on day 1 following the absorption of colostrum was not different from that of 0 h.

Table 1. Serum hepcidin, IgG, Lf, Fe and IL-6 levels of the pregnant cows
Tablo 1. Gebe ineklerin serum hepcidin, IgG, Lf, Fe ve IL-6 düzeyleri

Parameters	*Day -15*	*Day of Parturition ****	*P*
Hepcidin ng/mL	42.96±5.54	50.52±5.24	NS
IgG mg/dL	1793±64.59	1345±60.29	**
Lf ng/mL	191.9±25.85	337.6±42.27	*
Fe µg/dL	113.35±4.59	180.56±69.54	NS
IL-6 pg/mL	13.216±1.69	15.19±2.21	NS

* P<0.05, ** P<0.001, ***Blood samples taken shortly after birth. NS: Not significant.

Table 2. Hepcidin, IgG, Lf, Fe and IL-6 levels in milk and colostrum
Tablo 2. Kolostrum ve sütte hepsidin, IgG, Lf, Fe ve IL-6 seviyeleri

Parameters	*Colostrum (Day 0)*	*Milk (Day 1)*	*Milk (Day 3)*	*Milk (Day 7)*	*P*
Hepcidin ng/mL	84.06±2.24[a]	74.42±3.55[b]	75.43±2.07[b]	75.25±2.36[b]	*
IgG mg/dL	6282±397[a]	4118±263[b]	1733±79[c]	136±11[d]	**
Lf ng/mL	104967±15209[a]	89488±17460[ab]	60028±15076[b]	52034±4693[b]	*
Fe µg/dL	318±31[a]	82±11[b]	55±10[b]	52±10[b]	**
IL-6 pg/mL	11022±622[a]	498±55[b]	488±15[b]	-	**

* P<0.05, ** P<0.001.

Table 3. Alterations observed in the serum hepcidin, IgG, Lf, Fe and IL-6 levels of the neonatal calves
Tablo 3. Yenidoğan buzağıların serum hepsidin, IgG, Lf, Fe ve IL-6 seviyelerinde gözlenen değişiklikler

Parameters	*0 h*	*Day 1*	*Day 3*	*Day 7*	*Day 14*	*Day 28*	*P*
Hp ng/mL	58.17±3.24[cd]	84.52±1.82[a]	75.80±2.61[ab]	67.15±2.88[bc]	61.98±3.61[c]	50.43±4.15[d]	**
IgG mg/dL	47±6[a]	1534±110[de]	1592±121[e]	1320±97[cd]	1084±87[c]	820±74[b]	**
Lf ng/mL	184.93±24.68[a]	451.60±35.36[b]	352.68±22.13[c]	246.74±18.56[a]	235.81±21.35[a]	234.57±17.90[a]	**
Fe µg/dL	84.82±2.69[a]	98.82±2.97[ab]	63.19±5.59[d]	104.88±3.95[bc]	113.94±4.70[bc]	116.67±4.96[c]	**
IL-6 pg/mL	9.69±2.31[a]	17.85±2.46[b]	11.93±1.67[ab]	-	-	-	*

* P<0.05, ** P<0.001.

DISCUSSION

This study was designed to determine hepcidin, IgG, Lf, IL-6 and Fe levels in blood serum, colostrum, milk of healthy cows and healthy calves on different days of the neonatal period.

Starting from early pregnancy, Fe is required for placental and foetal development, increasing the number of maternal erythrocytes, and compensating for blood losses that occur during parturition. In the body, Fe is regulated by hepcidin (Koening et al., 2014). Studies carried out in obese pregnant women demonstrated that, while hepcidin levels were higher, the Fe levels in their cord blood were lower compared with lean controls. It was suggested that, the chronic inflammation and oxidative stress, which obese women suffer from, increase hepcidin levels, and thereby, impair the transfer of Fe to the foetus (Dao et al., 2013). Human research has shown that hepcidin levels measured at the beginning of gestation decrease as gestation advances (Finkenstedt et al., 2012; Van Santen et al., 2013). In the present study, it was determined that the hepcidin levels measured on the day of parturition were higher than the levels measured 15 days prior to parturition (Table 1). The differences between human researches and our study might be caused by differences in sampling days and species of concern. In our study, hepcidin levels measured shortly after birth were higher than 15 days prior to parturition. This might have been due to the opening of the cervix, vagina and vulva, and leaving the uterus exposed to pathogens and thus inflammation (Sheldon and Dobson, 2004). An increase in hepcidin levels during this period lowered the levels of Fe, which is a main nutritional source for pathogenic microorganisms (Vyoral and Petrak, 2005), and thereby, activated a non-specific defence mechanism.

In the present study, it was ascertained that the serum IgG levels on the day of parturition had significantly decreased in comparison to the levels measured 15 days prior to parturition (Table 1). This decrease was found to be in agreement with findings reported in previous studies (Detilleux et al., 1995; Franklin et al., 2005; Herr et al., 2011) and was attributed to colostrogenesis. Previous research suggests that the dry period, lactation period (Noaman et al., 2012; Noaman, 2014) and lactation number (Yokuş and Çakır, 2006) do not have any impact on serum Fe levels. In the present study, although the Fe and IL-6 levels on the day of parturition were found to have increased in comparison to the levels 15 days prior to parturition, these alterations were determined to be statistically insignificant (Table 1). The IL-6 levels determined in the present study were found to be similar to those reported by Ergönül and Kontaş Askar (2009). The results of the present study demonstrated significant increases in the Lf levels on the day of parturition, in comparison to the levels measured 15 days prior to parturition (Table 1). These significant increases were attributed to the stress caused by parturition, and Lf levels were considered to have increased due to the buffering function of this major antioxidant (Actor et al., 2009; Hidalgo et al., 2014). In addition, these increases are also thought to play a role in immunity to uterine infections due to restriction of Fe levels required to pathogens.

Previous reports shown that colostral IgG (Foley and Otterby, 1978; Blum and Hammon, 2000; Gomes et al., 2011), Lf (Sanchez et al., 1988; Blum and Hammon, 2000), Fe (Lönnerdal et al., 1981; Kume and Tanabe, 1993) and IL-6 (Hagiwara et al., 2000; Sobczuk-Szul et al., 2013) levels were high in colostrum and decrease with the conversion of colostrum into milk. Similar results have been obtained in the present study (Table 2). In the present study, colostral hepcidin levels were found to be significantly higher than the levels measured during the conversion of colostrum into milk (Table 2). We consider that this may be due to physiological changes in the composition of the colostrum.

Hepcidin levels in neonatal calves and alterations that occur in these levels with passive immunity have been investigated in this study. Accordingly, it was determined that the serum hepcidin levels on day 1 after the absorption of colostrum were significantly higher than the levels measured before colostrum absorption. The serum hepcidin levels were also determined to display a progressive decrease similar to serum IgG and Lf levels (Table 3). The alterations observed in the hepcidin levels were attributed to passively absorbtion like other biologically active substances, such as immunoglobulins and Lf.

It has been determined that serum IgG levels significantly increase 24 h after the absorption of colostrum, and start to decrease as from day 1 in calves (Abel Francisco and Quigley, 1993; Rocha et al., 2012). Such alterations were also observed in the present study (Table 3). This decrease in serum IgG levels has been attributed to the decrease of the absorption of macromolecules as a result of changes in the intestines, the secretion of digestive enzymes by intestinal cells over time, and the decrease of colostral IgG levels with each milking (Gökçe and Erdoğan, 2013). IgG, which is the main component of passive immunity in calves, was determined to reach its peak level on day 3, in the present study. Furthermore, it was observed that the hepcidin levels have similar changes like IgG on these days.

Some researchers have reported that Fe levels increase on the first day, but later display a progressive decrease until the 4^{th} week (Talukder et al., 2003). In another study, it was suggested that Fe levels decreased until the 4^{th} day, but started to increase as from the 2^{nd} week in calves (Klinkon and Ježek, 2012). In the present study, it was observed that the serum Fe levels had increased by the 24^{th} h, in comparison to the day 0, but had significantly decreased by day 3, when compared to the first two samplings (Table 3). These findings were found to be in agreement with those reported by Klinkon and Jezek (2012). It has been suggested that these decreases are due to the fact that hepcidin reduces the level of Fe required by microorganisms (Ganz, 2003; Singh et al., 2011). In the light of this data, it was considered that hepcidin played a role in the natural immunity of calves by showing a synergistic effect with IgG and Lf.

Holloway et al. (2002) suggested that no evidence existed between colostrum absorption and serum Lf levels. But Dawes et al. (2004) reported to have found Lf levels, before the absorption of colostrum, to be approximately 5 times lower than the levels measured at 24 h, in calves. Furthermore, these researchers determined a progressive decrease in Lf levels from the first day till the end of the neonatal period. In the present study, in calves, Lf levels reached their peak at 24 h, and progressively decreased until the end of the neonatal period. Similar changes were observed in serum IgG levels after from day 3 (Table 3). These data suggest that Lf play role in passive immunity.

Transfer of colostral cytokines to neonates has been reported to contribute to the strengthening of newborn immune functions (Yamanaka et al., 2003) The high level of cytokines found in the composition of colostrum is reported to activate neonatal immunity (Hagiwara et al., 2000). In the present study, it was determined that the serum IL-6 levels before the absorption of colostrum showed a two-fold increase at 24 h, but decreased on the 3rd day to the level measured before the absorption of colostrum in calves (Table 3). In our study, it was determined that changes due to colostrum absorption in IL-6 in calves were similar to those of Yamanaka et al. 2003.

As a result, hepcidin levels of calves has similar changes with IgG, Lf and IL-6 after colostrum absorption. These findings suggest that hepcidin could have a role in passive immunity in calves.

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