Case Report

Addition of dextrose and caffeine to the intravenous treatment of milk fever in Holstein Friesian cattle

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ABSTRACT

A farmer reported a cow unable to stand 48 hours postpartum. The cow was a 2.5 years old dairy cow with a body weight of around 350 kg. The cow was fed elephant grass, standard concentrate (16–18%) crude protein, and drinking water ad libitum without mineral supplementation during the dry season. The cow’s position and posture when lying down, ear temperature, and eye pupils were included in the physical examination. Availability of food and drink was examined to predict appetite and thirst. The results of the history and physical examination showed that the cow was unable to stand 48 hours after calving, had no appetite and eye reflexes, had cold ears, and trembling hind legs. The cow was laid on its right side, with its head turned to flank. Based on the anamnesis and physical examination, the cow was diagnosed as suffering from stage 2 puerperal hypocalcemia. The cow was infused via the jugular vein with a solution containing 270 mg calcium borogluconate, 70 mg magnesium borogluconate, 300 mg dextrose, 5 mg phosphorus element, 2 mg potassium chloride, and 5 mg caffeine per 1 mL of solution. Forty-five minutes after the infusion, the cow was able to stand, although it still looked weak. It could be concluded that the addition of dextrose and caffeine to the standard treatment of milk fever was beneficial for recovery.

Keywords: calcium, dextrose, puerperal hypocalcemia, magnesium, postpartum recovery

INTRODUCTION

The periparturient period (four weeks before and four weeks postpartum) significantly increased the risk of disease (DeGaris and Lean, 2008). This risk began with the high calcium requirements for fetal growth at the end of pregnancy (Saborío-Montero et al., 2017). Calcium requirements at the beginning of lactation also increase because each kg of milk contained 1.2 to 1.4 grams of calcium. Production of around two kilograms of milk required adequate utilization of all calcium in the blood. This was because sufficient amounts of calcium were needed to support high level of milk production (Mahen et al., 2018). Meanwhile, calcium in the blood was 8 to 10 mg/dl. In conditions where calcium in the feed was insufficient, calcium in the body will be mobilized to meet this need. If calcium levels in the blood could not be maintained, cows would experience puerperal hypocalcemia, paresis, or milk fever (Arechiga-Flores et al., 2022).

Puerperal hypocalcemia is a metabolic disorder in dairy cows that can occur before, during, or several hours up to 48 hours postpartum. This event was characterized by a sudden decrease in blood calcium levels from 9-
The incidence of clinical hypocalcemia in the field generally ranged 0-10%. However, cases of subclinical milk fever could exceed 25% in calving dairy cows. The percentage of cases of milk fever that occurred prepartum, during delivery, 1-24 hours postpartum, 25-48 hours postpartum and more than 48 hours postpartum were 3%, 6%, 75%, 12%, and 4% respectively (DeGaris and Lean, 2008).

Cows suffering from milk fever have a good prognosis if treated appropriately and as early as possible. Treatment measures are aimed at restoring calcium hemostasis and eliminating sharp drop in blood calcium in the process of calving. If treatment is carried out too late it can cause losses for farmers. The economic losses caused by milk fever consisted of drug costs, additional labor costs, decreased milk production, reproductive disorders, death and culling, as well as increased vulnerability of cows to metabolic and other infectious diseases (Probo et al., 2018). In addition, cows that experience milk fever were at risk of experiencing complications from other diseases, such as acidosis, ketosis, mastitis and displacement of the abomasum. Reproductive disorders could also occur after cases of milk fever in the form of retained placenta, metritis, and delays in uterine infusion (Venjakob et al., 2019). Losses due to subclinical hypocalcemia were estimated to be greater than clinical cases (Kocabagli, 2018).

Farmers could treat milk fever if the symptoms of the disease were still mild to moderate; However, if the symptoms of the disease are in the severe category, it should be immediately rejected or slaughtered because the treatment was not economical (Sudrajat et al., 2022). Studies regarding the handling of milk fever on smallholder farms are still rarely carried out. Standard treatment for milk fever prioritized intravenous administration of calcium borogluconate solution. The content of magnesium, phosphorus and potassium chloride salts in the infusion solution was supportive to help calcium absorption (Arechiga-Flores et al., 2022). Dextrose was a source of muscle-skeletal energy (Argilés et al., 2016), and caffeine was a neuro-muscular stimulant (Mesquita et al., 2020). Standard milk fever treatment with the addition of dextrose and caffeine has never been found in publications. Therefore, this study reports the treatment of milk fever in dairy cows with intravenous calcium borogluconate, magnesium borogluconate, dextrose, phosphorus, potassium chloride, and caffeine.

**MATERIALS AND METHODS**

A breeder at the Karya Bhakti Village Unit Cooperative, Ngancar district, Kediri regency, Indonesia reported that a Holstein Friesian cow could not stand 48 hours after postpartum. The cow was 2.5 years old and weighed around 350 kg. Anamnesis was obtained from the farmer regarding when the cow calved and since when the cow was unable to stand. The cow's body position and posture when lying down, ear temperature and eye pupils were included in the physical examination. Availability of food and drink was examined to predict appetite and thirst. Determination of the diagnosis was based on the stages of clinical symptoms that led to the diagnosis of milk fever, according to McArt et al. (2018). Based on the degree of severity, milk fever consisted of three stages. In prodromal stage (stage 1), serum calcium ranges from 6.5 to 8.0 mg/day. At this stage, the cow is restless. Appetite and output of urine and feces stops. Despite attempts to defecate, these attempts are unsuccessful. Cows quickly perceive external stimuli and are hypersensitive. The muscles of the head and legs appear trembling. In supine stage (stage 2), serum calcium ranges from 4.0 to 6.0 mg/day. At this stage, cows with milk fever cannot stand, lying on their stomachs with their heads facing backwards. As a result of dehydration, the skin appears dry and sluggish, the pupils are normal or dilated, and the response to light stimuli is slow or absent. The response to painful stimuli is also reduced, the muscles become flaccid, the anal sphincter relaxes, appetite is also lost, and the cow becomes more lethargic. In coma stage (stage 3) the cow is weak, unable to get up, and lies on its side (lateral recumbency). Weakened rumen muscles will soon be followed by a bloated rumen.
Circulatory disorders are very striking; the pulse becomes weak (120x/minute), and the body temperature drops below normal. The pupils dilate, and the light reflex disappears. This stage usually ends in death, even with conventional treatment (McArt et al., 2018).

Treatment in this case was carried out by intravenous administration of 270 mg calcium borogluconate, 70 mg magnesium borogluconate, 300 mg dextrose, 5 mg phosphorus element, 2 mg potassium chloride, and 5 mg caffeine per 1 mL of solution.

RESULTS

The anamnesis and physical examination showed that the cow was unable to stand 48 hours after calving, had no appetite and eye reflexes, had cold ears, and trembling hind legs. The cow lay down on the right side of the body and its head turned to the left behind the body. Based on clinical symptoms, the cow was diagnosed as suffering from hypocalcemia puerpuealis. The cow was unable to stand, lying on its stomach with its head tending to face backwards (Figure 2). Cow was given solution therapy containing 270 mg calcium borogluconate, 70 mg magnesium borogluconate, 300 mg dextrose, 5 mg phosphorus element, 2 mg potassium chloride, 5 mg caffeine, excipients q.s. ad 1 mL intravenously via the jugular vein (Figure 3). After being infused for 45 minutes, the cow was able to stand even though it looked weak.

DISCUSSION

Clinical symptoms of cows affected by milk fever included appetite, tetany, urination and defecation disorders, side lying position, coma, and death if left untreated (Tadesse et al., 2015). The case of milk fever in this study was in the second stage, possibly caused by a lack of calcium intake in the feed. Calcium varied from 0.80% in cows at the beginning of lactation, 0.70% in mid-lactation, 0.65% at the end of lactation, and 0.60% in the dry period (Chiwome et al., 2017). Milk fever (parturient paresis) is a metabolic disorder in dairy cows around calving time. Milk fever also caused cows to suffer from various other disorders. Calcium is needed for the release of acetylcholine at the neuromuscular junction (Khaziev et al., 2016), so that affected cows would begin to experience muscle weakness, be unable to stand, and eventually became comatose within a few hours (McArt et al., 2018). The risk of milk fever increased with decreasing magnesium and calcium intake and increasing phosphorus intake within a certain period of time before calving. Age increased the risk of milk fever by approximately 9% per lactation (DeGaris and Lean, 2008). The risk of developing milk fever was higher with increasing parity and higher levels of milk production (Chiwome et al., 2012).
in colostrum exceeded the intestinal absorption capacity-impaired absorption of Ca++ from the intestine during the puerperium. Slow mobilization of Ca++ from bone stores caused problems in maintaining normal serum levels (Kocabagli, 2018). During lactation, serotonin played a role in maintaining calcium homeostasis through the synthesis and secretion of parathyroid hormone-related protein (PTHrP), and this effect is independent of the action of parathyroid hormone (Arechiga-Flores et al., 2022). Integrative genome analysis showed that milk fever was associated with eight genomic regions on chromosomes BTA2, BTA3, BTA5, BTA6, BTA7, BTA14, BTA16, and BTA23. The CYP27A1, CYP2J2, GC, SNAI2, and PIM1 genes were directly involved in the activation, transport, and signaling of vitamin D. As is known,

![Figure 3 Intravenous injection of solution containing 270 mg calcium borogluconate, 70 mg magnesium borogluconate, 300 mg dextrose, 5 mg phosphorus element, 2 mg potassium chloride, and 5 mg caffeine (per mL solution).](image)

Vitamin D controlled calcium homeostasis. In addition, these genes also regulated calcium ion binding, calcium ion transport, T cell differentiation, B cell activation, protein phosphorylation, and apoptosis, which could cause milk fever (Pacheco et al., 2018). The case of milk fever in this study was caused by lack of sunlight exposure. Synthesis of vitamin D from pro Vitamin D required ultraviolet light from the sun. Vitamin D played a role in the process of calcium absorption. Milk fever could occur due to interference with vitamin D (Schaefer and Shoback, 2016). Vitamin D was needed to stimulate calcium absorption from the digestive tract. Vitamin D must first be converted into 25 hydroxy vitamin D in the liver, which required magnesium. Then it became 1.25-hydroxyvitamin D in the kidneys which required parathyroid hormone (Eder and Grundmann, 2022). Vitamin D functioned in calcium homeostasis and modulated the immune system.

Cows mobilized calcium for fetal growth during late gestation and milk production in early lactation, leading to lactational osteoporosis. Therefore, providing calcium for milk fever was greatly helped by vitamin D supplementation (McGrath et al., 2018). Vitamin D supplementation was essential to maintain milk production in dairy cows that were kept intensively in closed pens without exposure to direct sunlight (Hodnik et al., 2020).

Calcium metabolism is closely related to Magnesium and vitamin D. The relationship between magnesium and calcium metabolism could go through several pathways. The primary role of 1,25-dihydroxyvitamin D is its ability to stimulate active (trans-cellular) transport of dietary Ca across the small intestinal epithelium. Calcium can be absorbed from the lumen of the small intestine either through active or passive (paracellular) transport. Ca ion levels strongly influence passive (paracellular) transport in the intestinal lumen. Efficient Ca transport, namely when there is a lack of calcium from the feed, or the need for calcium is very high, occurs through active transport through the small intestinal epithelium. This transport process required 1,25-dihydroxyvitamin D to stimulate the formation of Calcium carrier proteins across the small intestinal epithelium. Magnesium played a role in the release of parathyroid hormone from the
parathyroid glands, then parathyroid hormone played a role in the mobilization and absorption of calcium (Fleet, 2017). If the parathyroid hormone released was insufficient, it would affect the mobilization of calcium from the bones. Magnesium played a role in the first step, namely the release of parathyroid hormone from the parathyroid glands; then, parathyroid hormone played a role in the second step, directly influencing calcium mobilization and absorption (Allgrove, 2015).

Milk fever treatment must be implemented immediately. The best option was to give calcium orally to cows that were still standing. Blood calcium levels increased for 30 minutes after administration and remain elevated for four to six hours later (Arechiga-Flores et al., 2022). Intravenous treatment rapidly increased blood calcium levels, but these increases could be extremely and potentially dangerous. It could cause fatal heart complications so it was not recommended to be given to cows that are still standing (Peek and Buczinski, 2018). After intravenous treatment, blood calcium levels decreased again to lower than-normal concentrations; as a result, the cow again showed hypocalcemia within a period of 12 to 18 hours. Even intravenous doses of calcium stopped the cow’s ability to mobilize the necessary calcium and meet the need at critical times. Experimentally, atropine-induced arrhythmias had been treated with alternating states of hypercalcemia and hypocalcemia in dairy cattle (Arechiga-Flores et al., 2022).

Milk fever in the second and third stages was treated with 500 mL of 23% calcium borogluconate solution which must be given immediately at a dose of 1 mL/kg bw intravenously, intramuscularly or subcutaneously (Braun et al., 2012). Intravenous calcium should be administered at a rate of approximately 1 g/min (4.3 mL/min) using a 16 g needle. This dose would supply 10.8 g/100 mL blood calcium to correct calcium deficiency (4-6 g/100 mL blood). Intravenous injection could be via the jugular vein or mammary vein and can be accompanied by subcutaneous administration. Administration of oral calcium 12 hours after recovery was carried out to avoid recurrence. This treatment aims to restore calcium levels in the blood as early as possible and prevented muscle and nerve damage due to cow lying down for too long (Arechiga-Flores et al., 2022; Aubineau et al., 2022). In this study, intravenous infusion of dextrose (a pure form of glucose) was used as an energy source for muscle contractions. Glucose transported to muscles entered glycolysis; through a series of enzymatic reactions, glucose underwent oxidation and the mitochondrial electron transport chain to produce ATP (Evans et al., 2019). Muscle contraction depended on the breakdown of adenosine triphosphate (ATP) and the release of free energy (Dunn and Grider, 2022).

In the milk fever case in this study, caffeine was also administered intravenously. Caffeine could increase muscle strength by increasing the capacity to release calcium ion [Ca^{2+}] concentration through sensitization of Ca^2+ channels, inducing the release of Ca^2+ from the sarcoplasmic reticulum (Ferreira et al., 2022). Caffeine is a Ca^{2+} ionophore, which improved skeletal muscle function. Caffeine increased myokine expression and secretion. The ergogenic effects of caffeine are mediated by myokine secretion due to increased [Ca2+] and/or AMPK activation (Takada et al., 2022). Caffeine stimulated AMPK activity and insulin-independent glucose transport, reducing muscle fatigue and increasing energy consumption during contractions (Tsuda et al., 2015). Caffeine promoted contraction-induced activation of the pentose phosphate pathway and increased IMP production. Caffeine also stimulated β-oxidation of fatty acyl-CoA, accompanied by increases in acyl-CoA, butyrylamine, and O-acetylcarnitine. However, this did not affect the glycolysis metabolites, glycerol-3-phosphate and L-lactic acid. Caffeine increased levels of amino acids associated with energy production (L-leucine, L-valine, and L-aspartate). Caffeine accelerated metabolic activation which causes increased muscle contractions thereby contributing to muscle endurance performance (Tsuda et al., 2019).

In this case, the cow was treated immediately to avoid complications. Milk fever could increase the risk of other diseases such as

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Acidosis, ketosis, mastitis, retained placenta, abomasum dysplasia, and endometritis (Kocabagli, 2018; McArt and Neves, 2019). Loss of uterine muscle tone due to hypocalcemia in cows suffering from hypocalemia is the main cause of uterine prolapse. Cows suffering from milk fever were six times more likely to experience dystocia than normal cows. This was caused by reduced contraction ability of smooth and skeletal muscles, causing dystocia (Tadesse et al., 2015).

As is known, calcium played a role in smooth muscle contractility. Hypocalcemia caused slower uterine involution, resulting in longer days open (Braga Paiano et al., 2019). Hypocalcemia caused an increased cortisol response that is periparturient immunosuppression. Apart from that, hypocalemia also reduced smooth muscle tone in the nipple sphincter, making it easier for infections in the mammary glands to cause of mastitis (Libera et al., 2021). Decreased immunity and opening of the reproductive tract postpartum also triggered endometritis. Hypocalcemia caused placental retention directly and indirectly. Hypocalcemia caused the tone and contractility of the myometrium to decrease so that it could not expel the placenta after calving. Hypocalcemia caused placental retention indirectly through dystocia. Dystocia is a risk factor for placental retention (Rodriguez et al., 2017). Hypocalcemia reduced rumen and abomasum motility so that it could cause rumen and abomasum dysplasia (Perween et al., 2018).

In general, preventing cases of milk fever is better than treating. Milk fever prevention strategies generally included acidifying the diet at the end of hypocalcaemic pregnancy and providing calcium at calving (Wilkens et al., 2020; Aubineau et al., 2022). Calcium homeostasis was controlled by calcitonin, parathyroid hormone, and vitamin D. Low prenatal calcium intake was initially thought to cause milk fever. Dietary cation-anion differentiation (DCAD) played a role in preventing calcium deficiency disorders (Melendez and Poock, 2017). The DCAD equation, which is an equation involving differences in food cation-anions which usually includes two cations (potassium and sodium) and two anions (chlorine and sulfur), could predict the risk of milk fever because the incidence of milk fever was linearly correlated with DCAD (DeGaris and Lean, 2008). The DCAD equation was milliequivalents (meq) \[\text{DCAD} = \frac{((\%K \text{ divided by 0.039}) + (\% \text{ Na divided by 0.023}) - ((\%\text{Cl divided by 0.0355}) + (\%\text{S divided by 0.016}))}{100 \text{ grams of food dry matter}}\] (Melendez and Chelikani, 2022).

Prevention of milk fever must involve the full participation of farmers in managing the health of dairy cows during the dry periods (Mills et al., 2020; Redfern et al., 2021). Apart from controlling nutritional intake during the dry period, monitoring peripartum blood calcium levels can be carried out periodically using noninvasive methods (Chiba et al., 2023). Additionally, farmers must also understand the symptoms of milk fever and be aware of the appearance of these symptoms in their dairy cows within 48 hours after calving.

**CONCLUSION**

Hypocalcemia in dairy cows was thought to be mainly caused by lack of nutritional (calcium and phosphorus) intake and lack of sun exposure. Hypocalcemia case in this study was categorized into stage 2; the cow could not stand, trembled, and tended to look back. Therapy with 270 mg calcium borogluconate, 70 mg magnesium borogluconate, 300 mg dextrose, 5 mg elemental phosphorus, 2 mg potassium chloride, and 5 mg caffeine intravenously helped the patient be able to stand after 45 minutes of treatment.

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**AUTHOR'S CONTRIBUTIONS**

Ady Kurnianto (AK), Novianto Meska Pratama (NMP). AK: handling the case and manuscript drafting. NMP: technical support in the handling the case. All authors read and

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CONFLICTS OF INTEREST
The authors report no conflicts of interest.

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