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Clinical efficacy of combinations of nebulised fluticasone, salbutamol and furosemide on lung function in premature calves with respiratory distress syndrome

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ABSTRACT: Surfactant deficiency, poor development of the lung structure and fibrosis as a result of inflammation are thought to play an important role in the development of respiratory distress syndrome in premature calves. Nebulised steroid (fluticasone), bronchodilator (salbutamol) and diuretics (furosemide) can be used in combination alongside standard treatment procedures for premature calves, and might improve viability as observed in infants, foals and horses with pulmonary disorders. Twenty-five premature calves with respiratory distress syndrome were used in this study. Oxygen and supportive treatment were administered to all groups. The first group was used as a control group (Group 1). The nebulised drug combinations were as follows: Group 2: fluticasone + salbutamol, Group 3: salbutamol + furosemide, Group 4: fluticasone + furosemide and Group 5: fluticasone + salbutamol + furosemide. During the 72-h time period of the study, fluticasone (15 μg/kg/12 h), salbutamol (0.025 mg/kg/6 h) and furosemide (1 mg/kg/12h) were applied for 5 min. Arterial blood samples were collected from the auricular artery at 0 h and at 1, 24, 48 and 72 h for blood gas analysis. Significant ($P < 0.05$) increases in arterial partial oxygen, oxygen saturation and peripheral oxygen saturation and decreases in arterial partial carbon dioxide, lactate and respiration rate were observed in all the nebulised treatment groups, while a statistical difference was observed only for arterial partial carbon dioxide in control group. When comparing the treated groups with the control, it may be concluded that nebulised drugs are highly effective in the therapy of premature calves with respiratory distress syndrome, while the different nebulised groups exhibited similar efficacies.

Keywords: calf; arterial blood gas; nebulised drugs; treatment

List of abbreviations

$PaCO_2$ = arterial partial carbon dioxide, **PaO_2** = arterial partial oxygen, **RDS** = respiratory distress syndrome, **$SatO_2$** = oxygen saturation, **SpO_2** = peripheral oxygen saturation

Calves born between days 230 and 260 of gestation are defined as premature (Ok et al. 2000; Guzelbektes et al. 2012). Premature calves suffer from life-threatening disorders associated with the incomplete development of organs including the brain, locomotor system, gastrointestinal tract and lungs (Bleul 2009; Altug and Basbugan 2013; Aydogdu et al. 2016). The final stages in the development of normal lungs are interrupted by premature birth resulting in reduced gas exchange capacity due to decreased lung volumes and capillary surface areas. Impaired gas exchange leads to

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hypoxaemia and the need to supplement oxygen (Kotecha 2000; Ok and Birdane 2000; Aydogdu et al. 2016). It is thought that surfactant deficiency, poor development of the lung structure and fibrosis as a result of inflammation may play important roles in the development of respiratory distress syndrome in preterm human infants (Murch et al. 1996; Lee et al. 1998).

Treatment with nebulised drugs is an established treatment for preterm and term infants. The inhalation of the drugs delivers the drug particles deep into the lung tissue. The administration of the drugs via inhalation has many advantages such as providing local effects, a general lack of systemic side effects, and its easy and quick usage. In this way, steroids, bronchodilators, diuretics and antibiotics can be delivered into the lungs (Muers 1997; Boe et al. 2001).

Corticosteroids increase the production of antioxidant enzymes and surfactant and reduce pulmonary inflammation, bronchospasm, bronchial oedema and fibrosis (Lipworth 1997; Bancalari at al. 2005). The most commonly administered corticosteroids via the inhalation route are fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide and flunisolide. Fluticasone propionate is an anti-inflammatory agent and is commonly administered by inhaler for the treatment of asthma. Fluticasone propionate is also widely used in the treatment of respiratory disorders in horses with inflammatory airway disease (Gray et al. 2013).

Diuretics reduce interstitial oedema, vascular resistance and oxygen consumption and facilitate gas exchange in the lungs (Abman and Groothius 1994; Bancalari et al. 2005). Furosemide is the most commonly used inhalation diuretic drug. The mechanism by which inhaled furosemide improves pulmonary function is not clearly understood, but several mechanisms have been reported previously by different researchers (Frizzel et al. 1975; Welsh 1983; Anderson et al. 1990; Moscato et al. 1991; Pavord et al. 1992).

Salbutamol is a short-acting β2-adrenergic receptor agonist which elicits the relaxation of smooth respiratory muscles. Bronchodilator therapy is effective in infants born preterm and is associated with improvements in lung function. A favourable response to the treatment has been described in ventilated infants (Sosulski et al. 1986; Wilkie and Bryan 1987). Inhalation treatment using nebulisers is frequently chosen to treat asthma and bronchopulmonary dysplasia of premature infants, foals and horses with chronic respiratory problems. There are no studies on the inhalation treatment of premature calves with respiratory distress syndrome (RDS).

We hypothesised that the administration of combinations of nebulised steroid (fluticasone), bronchodilator (salbutamol) and diuretics (furosemide) alongside standard treatment procedures in premature calves might increase the viability of the calves as has been observed in human infants, foals and horses.

MATERIAL AND METHODS

Animals. Twenty-five premature calves (five Simmental, two Brown Swiss and 18 Holstein breed) diagnosed with RDS were admitted to the Large Animal Clinic in the Faculty of Veterinary Medicine at Selcuk University between 2–12 h after birth. Premature calves were randomly assigned a number using a random number generator as follows: Group 1 (G1, n = 5), Group 2 (G2, n = 5), Group 3 (G3, n = 5), Group 4 (G4, n = 5), Group 5 (G5, n = 5). The first group (G1) was used as a control group, whereas the G2, G3, G4 and G5 were used as experimental groups. Primary clinical evaluation was performed and artificial insemination records were checked to ensure prematurity and to establish whether the calves met the RDS criteria specified below. The premature calves had a gestational age between 230 and 260 days, low body weight, weak or no sucking reflex, a short silky hair coat, soft hooves, general weakness, an inability to stand and incomplete eruption of the incisor teeth (Ok et al. 2000; Guzelbektes et al. 2012). Hypoxaemia (arterial partial oxygen (PaO_2) less than 60 mm Hg), hypercapnia (arterial partial carbon dioxide ($PaCO_2$) greater than 45 mm Hg), tachypnoea (respiratory rate greater that or equal to 45 breaths/min) and expiration accentuated by an abdominal lift were used as RDS criteria in premature calves (Verder et al. 1999; Bleul et al. 2008). The blood pressure, respiratory rate, oxygen saturation and body temperature of premature calves were monitored using a Compact 7 (Medical Econet, Germany) and observed clinically at 0 h (before treatment), and in the 1st, 2nd, 4th, 8th, 24th, 48th and 72nd hours of the study. Calves with RDS caused by other diseases were excluded from the study. The research procedure was carried out with the approval of the Institutional Ethics

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Committee of the Faculty of Veterinary Medicine, Selcuk University (decision No. 2013/039).

Standard treatment protocol for premature calves. Standard treatment including oxygen administration and supportive treatment was administered to each calf in all the groups.

Oxygen therapy. All premature calves received oxygen therapy (5–6 l/min per calf) via a mask. Oxygen supplementation was discontinued when oxygen saturation ($SatO_2$) was greater than 80% after 24 h of intranasal oxygen administration. If the $SatO_2$ remained under 80%, oxygen supplementation was reinstituted.

Supportive treatment and clinical care. Vitamin ADE (1 ml/day *i.m.*) (Ademin®, Ceva-Dif, Turkey), calcium (0.2 ml/kg/day *s.q.*) (Kalsimin®, Vilsan, Turkey), phosphorus (3 ml/day *s.q.*) (Fosfotonik®, Topkim, Turkey), erythromycin (10 mg/kg/day *i.m.*) (Erivet®, Biomed, Turkey) and vitamin C (3 ml/day *s.q.*) (Cevit®, Biovita, Turkey) were administered for three days, while a single dose of selenium-vitamin E (1 ml *i.m.*) (Yeldif®, Ceva-Dif, Turkey) was administrated to each calf. Isotonic sodium bicarbonate (0.9% NaCl (Ulugay, Turkey) and Bikarvil (Vilsan, Turkey)) and 5% dextrose (Dekstrosol, Vilsan, Turkey) were slowly infused to premature calves which, in $PaCO_2$ value measurements, were found to have pH values of less than 7.2 and base excess less than –3 mmol/l (Guzelbektes et al. 2012; Aydogdu et al. 2016). Fluids were administered only between the 2nd and 10th hour on the first day; only dextrose was administered on the second and third days to prevent changes in arterial blood gas values. Fluid treatment was stopped 12 hours prior to sample collection in all groups. A bed (Figure 1) was used to place the calves in sternal recumbency in order to improve gas exchange. The calves were brought to an appropriate temperature with towels and an infrared heater (Ufo-NL26EN, Ufo Isikla, Turkey) which was kept in the intensive care room during treatment. Premature calves received fresh or frozen colostrum (10% of body weight, divided into four feedings) during the first 72 h after birth. Calves with a weak suckle reflex received colostrum via a stomach tube instead of a nipple bottle. In cases where abdominal distension occurred, oral feeding was stopped and fluid treatment was continued.

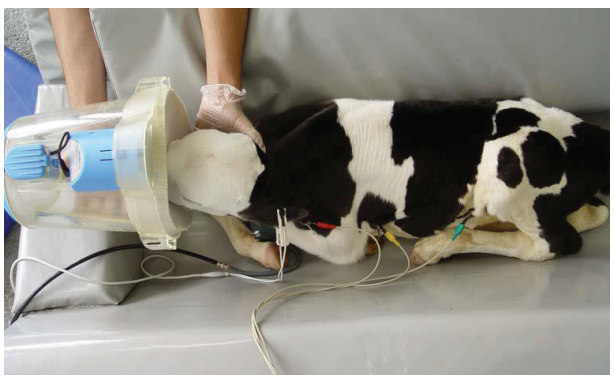

Figure 1. Nebulised drug admistration to premature calves

Nebuliser treatment protocol for premature calves. The following drug combinations were administered with a nebuliser: fluticasone + salbutamol for Group 2, salbutamol + furosemide for Group 3, fluticasone + furosemide for Group 4 and fluticasone + salbutamol + furosemide for Group 5. Fluticasone (15 µg/kg/12 h intervals over 72 h) (Flixotide®, GlaxoSmithKline, Australia), salbutamol (0.025 mg/kg/6 h intervals over 72 h) (Ventolin®, GlaxoSmithKline, Australia) and furosemide (1 mg/kg/12 h intervals during 72 h) (Diuril®, Vetas, Turkey) were diluted with 2.5 ml saline solution, and each drug was administered for 5 min with a nebuliser machine (NebuTech-SaHoMa®, Nebu-Tec Inter. med. Gmb, Germany) at regular intervals and sequentially (Fluticasone, Salbutamol, Furosemide) over the period of the experiment (72 h; Figure 1). The 0 h time point is "before treatment" and immediately after the blood sample was taken, the nebulised drugs were administered over the course of 10–15 min depending on the drug combination. Fluticasone and furosemide were administered six times, and salbutamol 12 times during the 72-hour treatment period.

Sample collection and blood analysis. Arterial blood samples were collected anaerobically from the auricular artery using sodium heparin-containing plastic insulin syringes, and blood gas analysis was performed within 10 min of collection. Insulin syringes were prepared by aspirating a small volume of liquid heparin (5000 IU/ml) (Nevparin®, Mustafa Nevzat, Turkey) and then expelling it. The thin film of liquid heparin that remains coated on the walls of syringe is sufficient to prevent the blood sample from coagulation. At least 0.6 ml were taken from each sample for blood gas analysis. The arterial blood pH, PaO_2, $PaCO_2$, base excess, lactate, glucose and oxygen saturation ($SatO_2$) were analysed using an automatic blood gas analyser (GEM Premier 3000, Inst. Laboratory, Lexington, USA) within 15 min after collection at 0 h (before treatment),

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and at 1, 24, 48 and 72 hours. Venous blood samples were taken from the jugular vein in order to measure the haemogram indices including white blood cells, red blood cells, haematocrit, haemoglobin and platelet count using an automatic haemocell counter (MS4e, Melet Schlosing Laboratories, France) within 15 min of sampling. The samples were taken at 0 h and at 24, 48 and 72 hours.

Statistical analysis. SPSS software for Windows, version 14.01 was used for the statistical analysis. All data are presented as mean values and include standard error of the mean (mean ± SEM). The distribution of the data was determined using the Kolmogorov-Smirnov test. A one-way ANOVA (post-hoc Duncan) test was used to compare the differences in the values between and within the groups. The level of significance was $P < 0.05$.

RESULTS

In our study, 20 out of 25 premature calves with RDS responded well to the therapy (80%) with 17 surviving calves (85%) in the nebulised treatment groups. In the clinical examination, apnoea or tachypnoea, weakness, cyanosis, increased capillary refill time, lack or absence of sucking reflex, hypothermia and depression were observed in all premature calves. Furthermore, visual disturbances, opisthotonus, depression, weakness of muscles and tendons, cyanotic or pale mucous membranes, failure to pass meconium combined with progressive abdominal distention, lethargy, coma and abdominal distension after feeding were also observed in the premature calves. During the treatment, an increase in awareness, a normalization of body temperature, sucking reflex, efforts to stand up with support and attempts to remain in the sternal position with support were the clinical findings observed within 24 h in the calves. In addition to these findings, a reduction in the frequency of wheezing and grunting sounds in respiration were observed up to the 48 h after treatment was commenced, and then costo-abdominal breathing, sucking reflexes and the ability to stand up and walk were also observed in these animals at the end of treatment. However, mild wheezing and grunting sounds were still audible from all calves at the end of the study.

The haemogram and arterial blood gas values are presented in Tables 1 and 2, respectively. The monitored parameters and clinical observations including peripheral oxygen saturation (SpO_2), mean arterial pressure, pulse rate, rectal temperature, and respiratory rate are presented in Table 3.

Group 1

A significant ($P < 0.05$) change was only determined in the concentration of $PaCO_2$ during the treatment period. Two calves did not respond to treatment, one calf died at 48 h and another at 72 h. In the non-surviving calves, the abdominal breathing pattern continued during treatment and sucking reflexes did not develop. One of the calves showed epistaxis, leukopaenia, thrombocytopaenia and ecchymosis on the skin at 24 h, and haemorrhage from the abomasum and forestomach was observed immediately after death.

Group 2

Significant ($P < 0.05$) increases in pH, base excess, PaO_2 and $SatO_2$ values (at 24, 48 and 72 h) and decreases in lactate (48 and 72 h) and $PaCO_2$ levels (24, 48 and 72 h) were observed in the calves in G2. One calf did not respond to treatment and died after 24 h.

Group 3

Significant ($P < 0.05$) increases in parameters (pH, base excess, PaO_2 and $SatO_2$) at 72 h and a decrease in lactate (24, 48 h) and $PaCO_2$ (24, 72 h) levels were determined in these calves. All premature calves in this group survived.

Group 4

Significant ($P < 0.05$) increases in pH (72 h), PaO_2 (24, 72 h) and $SatO_2$ (72 h) and a decrease in lactate (48 and 72 h) and $PaCO_2$ (1, 24, 48, 72 h) levels were determined. One calf did not respond to the treatment and died in 24 h.

Group 5

Significant ($P < 0.05$) increases in pH (48, 72 h), PaO_2 (24, 72 h) and $SatO_2$ (72 h), and decreases in

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Table 1. Haemogram parameters of groups (data are presented as mean ± SEM)

Parameters	Groups	Before treatment 0th h	After treatment 24th h	48th h	72nd h
White blood cells (10^3/μl)	G1	7.86 ± 1.81	6.20 ± 1.49	3.88 ± 0.75	6.25 ± 0.98
	G2	16.8 ± 4.94	10.5 ± 3.45	9.78 ± 3.36	9.92 ± 2.65
	G3	13.0 ± 2.65	7.91 ± 0.99	8.56 ± 0.90	8.46 ± 0.38
	G4	18.6 ± 10.9	11.7 ± 4.10	8.51 ± 2.62	11.6 ± 3.56
	G5	14.4 ± 6.20	5.41 ± 0.69	8.88 ± 4.27	5.75 ± 0.80
Red blood cells (10^6/μl)	G1	6.15 ± 0.49	5.09 ± 0.49	5.39 ± 0.49	5.50 ± 0.57
	G2	6.77 ± 0.48	6.10 ± 0.44	6.11 ± 0.44	5.98 ± 0.44
	G3	6.55 ± 0.43	5.53 ± 0.47	5.53 ± 0.47	5.57 ± 0.39
	G4	6.34 ± 0.36	5.54 ± 0.46	5.46 ± 0.39	5.66 ± 0.30
	G5	6.69 ± 0.49	6.47 ± 0.59	6.22 ± 0.43	6.06 ± 0.49
Haematocrit (%)	G1	25.6 ± 2.75	20.5 ± 2.30	21.5 ± 2.20	22.5 ± 2.90
	G2	32.4 ± 2.00[a]	27.5 ± 1.90[ab]	26.3 ± 1.67[b]	24.7 ± 1.35[b]
	G3	28.9 ± 2.12	24.0 ± 2.32	23.2 ± 1.84	22.9 ± 1.73
	G4	26.5 ± 1.42[a]	22.5 ± 1.88[ab]	20.5 ± 1.77[b]	21.2 ± 1.71[ab]
	G5	26.3 ± 2.34	19.0 ± 4.31	24.6 ± 1.97	22.5 ± 1.64
Haemoglobin (g/l)	G1	86.0 ± 7.50	70.2 ± 6.30	75.4 ± 7.00	78.2 ± 8.6
	G2	95.0 ± 5.60	85.6 ± 4.10	86.7 ± 3.70	87.4 ± 5.40
	G3	96.0 ± 7.20	81.2 ± 7.50	78.8 ± 7.50	79.4 ± 7.80
	G4	88.2 ± 3.20[a]	75.2 ± 5.80[ab]	72.2 ± 3.60[b]	76.5 ± 3.40[ab]
	G5	102 ± 15.4	81.0 ± 9.10	86.7 ± 5.80	80.0 ± 8.10
Platelet count (10^3/μl)	G1	145 ± 26.1	100 ± 11.3	114 ± 15.1	154 ± 28.7
	G2	261 ± 30.9	228 ± 78.7	242 ± 74.5	273 ± 71.3
	G3	202 ± 48.3	163 ± 47.1	207 ± 52.0	307 ± 114
	G4	224 ± 49.5	182 ± 42.4	218 ± 31.9	281 ± 45.5
	G5	185 ± 24.4	177 ± 12.6	196 ± 28.9	194 ± 21.5

[a,b]Letters in the same row are statistically significant ($P < 0.05$)

lactate (48 and 72 h) and $PaCO_2$ (24, 48, 72 h) levels were determined. One calf did not respond to treatment and died in 24 h.

pH values were elevated in all groups when G1 and nebuliser groups were compared; the pH values of G2 and G4 were increased ($P < 0.05$) at 48 and 72 h but no significant difference was determined among the nebuliser groups (Table 2).

The values of $PaCO_2$ were decreased ($P < 0.05$) in all groups. When G1 and nebuliser groups were compared, the $PaCO_2$ values of G2 and G4 were significantly ($P < 0.05$) decreased at 48 and 72 h, respectively. No differences were determined among nebuliser groups (Table 2).

In the nebuliser groups, pronounced increases in values of PaO_2, base excess, $SatO_2$ and decreases in lactate were observed, but no statistically significant differences were found among the groups (Table 2).

High lactate (> 10 mmol/l) and $PaCO_2$ (> 74 mg Hg), low PaO_2 (< 30 mg Hg), $SatO_2$ (< 30%) levels and hypoglycaemia (< 25 mg/dl) were determined in all of the non-surviving calves before death. A continuous abdominal breathing pattern, high breathing rate (> 74/min), lack of sucking reflex, abdominal distension after feeding and low body temperature (35–37 °C) were common clinical symptoms observed in the non-surviving calves. Post-mortem findings in these calves included widespread atelectasis and oedema in the lungs. In the gastrointestinal system, there was ulceration, bleeding and oedema in both the abomasum and intestines. Abomasum also contained undigested milk in all of the dead calves.

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Table 2. Arterial blood gas parameters of groups. Data are presented as mean ± SEM

Parameters	Groups	Before treatment 0th h	After treatment 1st h	24th h	48th h	72nd h
pH	G1	7.18 ± 0.10	7.17 ± 0.11	7.34 ± 0.04	7.34 ± 0.06^{B}	7.30 ± 0.11^{B}
	G2	7.29 ± 0.04^{b}	7.30 ± 0.04^{b}	7.41 ± 0.07^{ab}	7.49 ± 0.00^{aA}	7.49 ± 0.00^{aA}
	G3	7.39 ± 0.04	7.36 ± 0.03	7.44 ± 0.02	7.44 ± 0.01^{A}	7.43 ± 0.01^{AB}
	G4	7.19 ± 0.11^{b}	7.22 ± 0.09^{b}	7.37 ± 0.06^{ab}	7.45 ± 0.02^{abA}	7.52 ± 0.02^{aA}
	G5	7.18 ± 0.08^{b}	7.24 ± 0.07^{ab}	7.40 ± 0.41^{ab}	7.42 ± 0.02^{aAB}	7.42 ± 0.02^{aAB}
Partial pressure of arterial carbon dioxide (mmHg)	G1	56.2 ± 3.21^{a}	50.4 ± 3.23^{ab}	43.8 ± 1.93^{b}	45.2 ± 2.13^{bA}	47.0 ± 4.18^{bA}
	G2	52.0 ± 5.35^{a}	44.8 ± 5.22^{ab}	35.2 ± 3.80^{b}	38.5 ± 1.70^{bB}	38.5 ± 1.32^{bAB}
	G3	50.0 ± 3.18^{a}	37.8 ± 5.05^{b}	38.0 ± 0.70^{b}	40.5 ± 1.19^{abAB}	40.0 ± 1.22^{bAB}
	G4	59.2 ± 5.26^{a}	48.6 ± 3.65^{b}	43.6 ± 1.60^{bc}	44.7 ± 1.88^{bcAB}	37.0 ± 3.82^{cB}
	G5	64.7 ± 3.68^{a}	53.8 ± 8.18^{b}	40.3 ± 4.97^{b}	44.6 ± 2.33^{bAB}	42.0 ± 1.15^{bAB}
Partial pressure of arterial oxygen (mmHg)	G1	36.2 ± 5.49	32.8 ± 4.35	46.8 ± 5.86	39.7 ± 3.52	44.0 ± 4.18
	G2	28.4 ± 3.52^{c}	32.2 ± 4.61^{bc}	47.0 ± 8.20^{ab}	52.0 ± 5.90^{a}	60.2 ± 5.73^{a}
	G3	34.7 ± 2.65^{b}	45.2 ± 6.22^{ab}	43.8 ± 2.95^{ab}	44.2 ± 4.53^{ab}	52.0 ± 6.42^{a}
	G4	29.2 ± 5.54^{b}	31.0 ± 4.63^{b}	46.7 ± 4.66^{a}	42.0 ± 4.81^{ab}	50.2 ± 3.54^{a}
	G5	30.2 ± 5.15^{b}	42.0 ± 5.90^{ab}	51.5 ± 8.27^{a}	42.3 ± 4.25^{ab}	54.6 ± 6.33^{a}
Base excess (mmol/l)	G1	−5.14 ± 4.98	−5.90 ± 4.76	−0.38 ± 3.54	0.47 ± 4.18	−0.97 ± 5.34
	G2	−3.72 ± 0.87^{c}	−4.14 ± 1.14^{c}	0.80 ± 1.80^{b}	6.12 ± 0.57^{a}	5.55 ± 0.54^{a}
	G3	1.68 ± 2.24^{a}	−4.16 ± 1.87^{b}	3.68 ± 2.67^{a}	3.78 ± 0.68^{a}	3.64 ± 1.22^{a}
	G4	−9.82 ± 4.85^{b}	−5.80 ± 6.28^{ab}	5.07 ± 2.88^{a}	6.95 ± 1.83^{a}	6.52 ± 2.08^{a}
	G5	−2.86 ± 2.94	0.90 ± 1.73	2.32 ± 1.40	4.20 ± 1.31	3.05 ± 1.43
Oxygen saturation (%)	G1	49.8 ± 12.4	43.4 ± 12.6	75.8 ± 6.47	69.0 ± 5.98^{B}	70.7 ± 13.9
	G2	45.0 ± 8.77^{c}	51.8 ± 10.4^{bc}	76.0 ± 14.2^{ab}	88.0 ± 2.54^{aA}	91.7 ± 1.97^{a}
	G3	61.6 ± 5.83^{b}	77.6 ± 7.35^{a}	81.2 ± 2.63^{a}	79.2 ± 5.00^{aAB}	86.8 ± 3.03^{a}
	G4	47.6 ± 12.4^{b}	54.0 ± 14.3^{b}	73.8 ± 8.40^{ab}	77.5 ± 5.72^{abAB}	88.2 ± 2.56^{a}
	G5	43.8 ± 12.9^{b}	65.0 ± 10.6^{ab}	80.5 ± 7.66^{a}	77.3 ± 7.17^{abAB}	88 ± 2.64^{a}
Lactate (mmol/l)	G1	7.36 ± 3.03	7.42 ± 3.02	5.32 ± 2.61	5.05 ± 3.32	4.85 ± 3.38
	G2	7.62 ± 1.96^{a}	7.42 ± 1.65^{a}	4.08 ± 1.15^{ab}	1.60 ± 0.26^{b}	1.32 ± 0.32^{b}
	G3	3.94 ± 0.84^{ab}	6.18 ± 1.29^{a}	3.20 ± 0.94^{b}	1.42 ± 0.21^{b}	1.68 ± 0.46^{b}
	G4	8.42 ± 1.91^{a}	8.20 ± 1.05^{a}	5.02 ± 2.52^{ab}	2.22 ± 0.48^{b}	1.50 ± 0.33^{b}
	G5	8.02 ± 2.12^{a}	5.92 ± 0.97^{ab}	4.25 ± 1.51^{ab}	2.80 ± 1.71^{b}	1.30 ± 0.50^{b}
Glucose (mmol/l)	G1	3.03 ± 0.70	3.35 ± 0.40	3.62 ± 0.94	3.01 ± 0.91	5.12 ± 0.57
	G2	2.13 ± 0.73^{b}	2.69 ± 0.64^{ab}	4.54 ± 0.78^{a}	4.61 ± 0.48^{a}	4.73 ± 0.63^{a}
	G3	2.68 ± 0.76^{b}	4.34 ± 0.73^{ab}	5.23 ± 0.46^{a}	4.45 ± 0.74^{ab}	4.82 ± 0.89^{ab}
	G4	2.40 ± 0.68^{b}	3.43 ± 0.83^{ab}	4.55 ± 0.75^{ab}	5.22 ± 0.15^{a}	4.40 ± 0.83^{ab}
	G5	2.08 ± 0.47^{b}	3.33 ± 0.49^{ab}	3.80 ± 0.65^{a}	4.88 ± 0.58^{a}	4.53 ± 0.46^{a}

^{a,b}Letters in the same row are statistically significant ($P < 0.05$)

^{A,B}Letters in the same column are statistically significant ($P < 0.05$)

DISCUSSION

The insufficient production of surfactant in the lungs of preterm infants causes RDS, which increases the mortality and morbidity rates (Mariani and Carlo 1998). The main purpose of the treatment of RDS is the control of respiratory failure. Thus, its treatment includes supportive care such as oxygen and specific treatment for the lungs (Ovali 2007; Bleul 2009). The application of surfactant is one of

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Table 3. Monitoring and clinical parameters of the groups. (dta are presented as mean ± SEM)

Parameters	Groups	Before treatment 0th h	After treatment						
			1st h	2nd h	4th h	8th hour	24th h	48th h	72nd h
Peripheral oxygen saturation (%)	G1	69.8 ± 7.68	73.4 ± 6.61	76.2 ± 6.82	72.8 ± 7.00	85.2 ± 4.35	85.2 ± 3.27	84.7 ± 5.40	83.5 ± 4.62^{B}
	G2	68.8 ± 3.18^{d}	75.4 ± 4.41^{cd}	67.7 ± 5.48^{d}	79.5 ± 6.94^{bcd}	84.8 ± 5.45^{abc}	89.8 ± 1.56^{ab}	92.5 ± 2.72^{ab}	93.5 ± 0.28^{aA}
	G3	74.6 ± 3.23^{d}	80.8 ± 1.95^{c}	83.4 ± 2.56^{bc}	86.4 ± 3.10^{abc}	89.0 ± 1.30^{ab}	91.4 ± 1.07^{a}	92.4 ± 0.40^{a}	91.4 ± 0.40^{aA}
	G4	69.8 ± 1.42^{d}	76.6 ± 1.56^{c}	81.2 ± 1.06^{b}	83.0 ± 1.34^{b}	90.2 ± 1.10^{a}	90.6 ± 0.40^{a}	90.5 ± 0.50^{a}	90.2 ± 0.25^{aA}
	G5	63.2 ± 2.26^{c}	79.2 ± 1.68^{b}	83.6 ± 2.06^{ab}	86.4 ± 2.69^{a}	88.6 ± 2.22^{a}	89.6 ± 2.24^{a}	89.2 ± 1.70^{a}	90.5 ± 1.19^{aA}
Temperature (°C)	G1	35.1 ± 1.40	35.3 ± 1.41	35.3 ± 1.35	36.2 ± 1.00	36.8 ± 0.88	37.6 ± 0.66	36.8 ± 0.95	37.4 ± 0.90
	G2	36.2 ± 0.96	36.4 ± 1.03	36.7 ± 1.09	37.4 ± 1.07	37.4 ± 0.59	37.9 ± 0.56	38.3 ± 0.16	38.4 ± 0.12
	G3	34.6 ± 2.91^{b}	37.7 ± 0.45^{ab}	37.7 ± 0.45^{ab}	37.7 ± 0.39^{ab}	37.9 ± 0.16^{ab}	38.4 ± 0.23^{a}	38.2 ± 0.22^{a}	38.1 ± 0.30^{ab}
	G4	34.6 ± 1.10^{b}	35.0 ± 0.92^{b}	36.2 ± 1.28^{ab}	36.4 ± 0.76^{ab}	35.8 ± 1.01^{ab}	37.3 ± 0.57^{ab}	38.5 ± 0.46^{a}	38.4 ± 0.32^{a}
	G5	35.1 ± 0.86^{c}	36.4 ± 0.59^{bc}	36.8 ± 0.72^{abc}	38.8 ± 0.40^{ab}	37.7 ± 0.34^{ab}	38.2 ± 0.39^{ab}	38.2 ± 0.49^{ab}	38.5 ± 0.31^{a}
Respiratory rate (minute)	G1	60.2 ± 5.35	63.0 ± 7.23	66.4 ± 8.23	69.6 ± 9.26	70.0 ± 8.83	64.0 ± 8.67^{A}	50.4 ± 6.70	59.0 ± 4.79^{A}
	G2	68.0 ± 7.11^{a}	65.2 ± 11.2^{ab}	50.4 ± 8.28^{abc}	49.3 ± 14.4^{abc}	60.0 ± 3.74^{abc}	40.4 ± 5.03^{bcB}	40.7 ± 6.0^{bc}	36.0 ± 4.89^{cB}
	G3	51.8 ± 8.80^{a}	52.0 ± 8.02^{ab}	48.0 ± 5.47^{b}	49.6 ± 6.49^{b}	44.0 ± 5.89^{ab}	42.0 ± 4.89^{bAB}	40.4 ± 7.87^{b}	37.4 ± 3.28^{bB}
	G4	62.2 ± 5.64^{a}	60.6 ± 7.69^{ab}	55.8 ± 7.70^{abc}	50.0 ± 6.35^{abc}	49.2 ± 5.42^{abc}	40.4 ± 5.03^{bcB}	40.7 ± 6.01^{bc}	36.0 ± 4.98^{cB}
	G5	70.0 ± 8.16^{a}	68.0 ± 8.20^{ab}	63.6 ± 6.88^{b}	67.0 ± 7.72^{ab}	55.3 ± 3.52^{a}	50.5 ± 7.63^{bAB}	46.0 ± 7.43^{b}	38.0 ± 5.35^{bB}
Mean arterial pressure (mmHg)	G1	84.6 ± 10.0	79.5 ± 8.53	65.7 ± 4.21	72.0 ± 6.96	83.2 ± 5.64	80.7 ± 7.31	93.2 ± 7.37	94.7 ± 16.3
	G2	76.5 ± 6.88	85.6 ± 2.83	91.2 ± 6.20	77.0 ± 10.7	78.0 ± 8.69	86.5 ± 8.84	85.6 ± 9.45	82.2 ± 5.26
	G3	97.6 ± 7.24	90.4 ± 4.73	92.0 ± 9.20	85.2 ± 1.98	84.2 ± 2.35	99.4 ± 6.50	89.2 ± 6.11	85.6 ± 4.27
	G4	79.8 ± 2.20	83.0 ± 3.22	83.7 ± 5.54	82.0 ± 5.61	84.0 ± 3.67	81.2 ± 8.61	95.0 ± 3.00	87.5 ± 4.48
	G5	81.8 ± 6.20	87.8 ± 6.19	81.0 ± 6.34	92.2 ± 4.04	86.7 ± 6.65	92.7 ± 7.78	96.0 ± 4.58	87.5 ± 8.65

^{a,b,c}Letters in the same row are statistically significant ($P < 0.05$)

^{A,B}Letters in the same column are statistically significant ($P < 0.05$)

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the specific treatments and it is considered to be the standard treatment for premature newborns with RDS (Gomella 2004). Commercially available human surfactant products contain calf or porcine surfactants or synthetic components which are very expensive (Bleul 2009). Karapinar and Dabak (2008) administered 100 mg/kg surfactant to premature calves: the survival rates in the premature calves were found to be 0% and 60% in animals that did not or did receive surfactant, respectively. Bleul (2009) reported that the cost of commercially available surfactant products makes their usage virtually impossible in calves. For instance, in a 40-kg body weight calf (100 mg/kg dose surfactant), treatment with Curosurf (Chiesi Farmaceutici, Parma, Italy) costs about $12,000, whereas a single treatment with Survanta (Abbott Laboratories, Abbott Park, USA) costs approximately $16,000 in the United States. Therefore, the usage of surfactants in the treatment of ruminants is prohibitively expensive, and less costly drugs for the special treatment of the lungs are urgently needed in veterinary practice for preterm ruminants. In our study, the cost of nebulised drugs in addition to standard therapy was about $5 per 72-h treatment per calf.

Nebuliser drug delivery may be described as a special treatment and nebulisers are inexpensive and available from human medical supply companies. Reduction of inflammation, enhancement of mucociliary clearance, control of infection and reduction in the viscosity of aspiration are all potential benefits of nebuliser treatment (Morresey 2008). Drugs such as steroids, diuretics and bronchodilators are commonly used with nebulisers for the treatment of RDS in humans and horses (Broadstone et al. 1991; Muers 1997; Fok et al. 1999; Boe et al. 2001). However, there is no published report of nebuliser treatment in premature calves with RDS.

Steroids exert beneficial effects due to the fact they stimulate the production of surfactant proteins A and D (Wang et al. 1996) and antioxidant enzymes that decrease bronchospasm, pulmonary oedema, fibrosis, responses of inflammatory cells and mediators in the undeveloped lungs of premature infants (Yeh et al. 1998; O'Shea et al. 1999; Bancalari et al. 2005). Inhaler corticosteroids significantly improve the functional residual capacity and alleviate respiratory symptoms (Yuksel and Greenough 1992). Nebulised salbutamol, a bronchodilator, has an immediate benefit and improves lung function in preterm infants (Yuksel and Greenough 1991; Yuksel and Greenough 1994). Pai and Nahata (2000) reported that inhaled furosemide (1–2 mg/kg) improved pulmonary function in preterm neonates without significant adverse effects. It was also reported that the administration of aerosolized furosemide (1 mg/kg) significantly decreased pulmonary resistance and increased dynamic compliance, but had no effect on PaO_2 or $PaCO_2$ in ponies with airway obstruction (Broadstone et al. 1991).

One of the reliable methods of evaluating pulmonary function is the determination of the $PaCO_2$ and PaO_2 of arterial blood (Bleul et al. 2007). An arterial PaO_2 of less than 60 mm Hg is considered as a sign of RDS in human infants and foals (Verder et al. 1999; Knottenbelt et al. 2004; Bleul 2009). Foals with $PaO_2 < 55$ mm Hg during treatment have previously been reported to have a poor prognosis (Knottenbelt et al. 2004). In our study, PaO_2 values were over the 50.2 ± 3.54 mm Hg level at 72 h, but only in G2 were values significantly elevated above this value, to 60.2 ± 5.73 mmHg (Table 2). In healthy calves, PaO_2 levels were reported to range between 47.8 ± 17.8 and 58.1 ± 13.1 after birth and for calves with RDS, the PaO_2 levels were found to be between 29.7 ± 12.9 and 38.4 ± 8.8 one hour after birth (Bleul 2009). A partial pressure of oxygen below the 45-mmHg level together with pertinent clinical signs are most likely pathognomonic for RDS (Bleul 2009). In this study, the mean values of PaO_2 levels at 0 h were between 28.4 ± 3.52 and 36.2 ± 5.49 mmHg in all of the treatment groups (Table 2). These animals had respiratory difficulty, which can be considered as pathognomonic for RDS in premature calves. The mean value of PaO_2 in G1 at 72 h was determined to be 45 ± 4.18 mm Hg, and the mean respiration rate (59 RR/minute) did not return to a normal level. This shows that pathognomonic signs continued during treatment in Group 1. In the fluticasone and salbutamol treatment group (G2), PaO_2 levels increased to 60.2 ± 5.73 mmHg, and RR/minute values decreased to 36.0 ± 4.89 at 72 h (Tables 2 and 3), indicating effective improvement in the pulmonary function of premature calves with RDS. These results are in accordance with previous findings; inhaled fluticasone and salbutamol treatments were reported to influence airway resistance and lung volume (Yuksel and Greenough 1994), lung compliance (Fok et al. 1999) and improve the functional resid-

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ual capacity (Yuksel and Greenough 1992). The respiratory morbidity of preterm infants is associated with a high airway resistance (Yuksel et al. 1991) and reduced functional residual capacity (Yuksel and Greenough 1991). Inhaled corticosteroids significantly improve the functional residual capacity and alleviate the respiratory symptoms (Yuksel and Greenough 1992) in preterm infants. Fok et al. (1999) reported that early treatment with inhaled fluticasone resulted in a better improvement in lung compliance than in the placebo group and may be beneficial to ventilated preterm infants with RDS in a similar way to the early use of systemic dexamethasone. Yuksel and Greenough (1994) concluded that inhaled bronchodilator therapy results in significant beneficial effects on airway resistance and lung volume in preterms. Robertson and Bailey (2002) administered salbutamol (2 mg/kg) to anaesthetised horses with PaO_2 values of less than 70 mm Hg; this resulted in an almost two-fold increase in PaO_2 values within 20 min of treatment while no changes in heart rate or mean arterial blood pressure were associated with salbutamol.

Oxygen therapy is indicated in any neonate with a PaO_2 less than 60 mmHg or $SatO_2$ less than 90%. The goal of oxygen therapy is to maintain the PaO_2 from 80 to 110 mmHg and $SatO_2$ at greater than 92% (Palmer 2005). Bleul et al. (2007) reported that the highest values for $SatO_2$ in neonatal calves with RDS were 82 ± 15% during a 12-h intranasal oxygen supplementation. In the present study, the $SatO_2$ rates in the nebuliser treatment groups were greater than 85% at 72 h. Specially, $SatO_2$ levels at 72 h were greater than 90% only in calves which received a fluticasone and salbutamol combination (G2). However, $SatO_2$ levels in Group 1 had not risen above 70% by the end of the treatment. Gomella (2004) reported that arterial oxygen saturation should be kept between 88–95% in neonatal infants. However, in human medicine, such high target (92%) values are controversial and values of between 70% and 90% are recommended to prevent the adverse effects associated with oxygen administration (Tin et al. 2001). Similarly, Bleul (2009) recommended that an oxygen saturation of 70% to 90% should also be the target in calves that respond to oxygen administration. The $SatO_2$ values in the nebuliser treatment groups in our study are consistent with previous reports (Uysteprusyt et al. 2000; Gomella 2004; Palmer 2005), but the Group 1 showed oxygen levels below the specified values. The low levels of $SatO_2$ in the Group 1 indicate that the standard treatment alone may not be sufficient to increase $SatO_2$ up to the recommended levels (Palmer 2005). On the other hand, an inhaled fluticasone and salbutamol combination in addition to the standard treatment seems to be sufficient to increase $SatO_2$ to recommended levels in premature calves with RDS. In the present study, changes in SpO_2 values paralleled changes in $SatO_2$ values in premature calves (Table 3). In addition, we noted that many factors affect the measurement of SpO_2 values (shaving and thermoregulation of ear and mouth, movement, severe cyanosis, etc.) and for reliable results the measurements must be repeated a few times.

It is commonly accepted that the determination of pH and base excess are valuable indicators for detecting mixed metabolic and respiratory acidosis in calves after birth (Eigenmann at al. 1984; Szenci 1985). In our study, blood pH values in the Group 1 were below the normal values (pH < 7.35) after 72 h. This might be due to the continuation of CO_2 retention with hyperlactatemia in Group 1. Carbon dioxide levels increase in the blood when elimination is impaired by insufficient vital capacity, and results in respiratory acidosis in premature calves with RDS (Bleul et al. 2007). Reduction in pH is caused by the accumulation of carbon dioxide (CO_2) which cannot be adequately eliminated from the blood in immature calves with RDS. When the value of $PaCO_2$ rises above 45 mmHg this indicates RDS (Bleul et al. 2008). In the present study, the levels of $PaCO_2$ were found to be greater than 50 mmHg (mean value 50 to 74 mmHg) in all groups at 0 h (Table 2). A significant decrease in $PaCO_2$ values was observed in all of the nebuliser treatment groups with the highest decreases in $PaCO_2$ obtained in Group 2 and Group 5 at the end of the treatment (Table 2). Blood $PaCO_2$ and lactate concentrations were suggested to be useful metabolic markers for the determination of tissue hypoxia in infants (Nanda and Suresh 2009; Boode 2010). It has been reported that blood lactate concentrations of between 2 and 4 mmol/l should be interpreted with caution, whereas values above 4 mmol/l are indicative of a clinically important disruption of oxygen transport and cellular metabolism; plasma lactate concentrations above 4 mmol/l in cattle with pneumonia indicate that death will occur within 24 h (Coghe et al. 2000; Radostits 2000). In the present study, mean lactate levels at 0 h in all groups ranged between 3.94 and 8.42 mmol/l, which were

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high compared to the normal values of healthy calves (< 2 mmol/l; Table 2). Lactate concentrations were significantly decreased during treatment and mean levels at 72 h (end of the treatment) were found to be within the normal range (< 2 mmol/l) in nebuliser treatment groups. Lactate concentrations in the Group 1 showed no significant reduction during the treatment and were found to be above the critical value (> 4 mmol/l) at the end of the treatment. All of the premature calves in the Group 3 in which lactate concentrations were less than 4 mmol/l before the treatment (0 h) also survived after nebulised treatment. Blood $PaCO_2$ and lactate concentrations were reported to be associated with increased mortality in preterm human newborns with RDS (Yoxall and Wendling 1996; Boode 2010). In the study of Beca and Scopes (1972), all preterms with lactate concentrations < 3.9 mmol/l survived but preterm human infants with rising lactate values died, even when initial values were normal. Yildiz et al. (2017) reported that mean lactate concentrations were 9.5 mmol/l in non-surviving and 5.1 mmol/l in surviving premature calves with RDS. In the present study, premature calves with RDS which had lactate concentrations greater than 10 mmol/l died. Evaluation of mortality in premature calves with RDS was also determined by considering the optimal parameters such as $PaCO_2$ and lactate levels. High lactate (> 10 mmol/l) and $PaCO_2$ (> 74 mg Hg) concentrations were found to be indicative of a high risk of death in premature calves with RDS. Thus, lactate level seems to be a suitable prognostic value for monitoring premature calves with RDS. Hypothermia and hypoglycaemia are also important clinical findings in dead calves, and, thus, these were monitored during the treatment period of premature calves with RDS.

In the present study, post-mortem findings in non-surviving calves were widespread atelectasis and oedema in the lungs, ulceration, bleeding and oedema in abomasum and intestine. In addition to these findings, the abomasum was full in all of the non-surviving premature calves with RDS. These findings reveal that major gastrointestinal problems, in addition to lung disorders, also occur in premature calves with RDS. In the present study, therefore, post-mortem findings observed after the death of premature calves were similar to those reported in earlier studies (Furr et al. 1992; Bleul et al. 2008). Bleul et al. (2008) reported that abnormal pulmonary function was not the only critical factor in the premature calves. Inflammation of the mucosa of the forestomach and abomasum and pulmonary infection should also be taken into consideration when treating these animals.

The results of the present study show that nebulised treatment had beneficial effects on lung function in premature calves with RDS. Furthermore, these effects are most probably elicited by the inhaled fluticasone and salbutamol used in the study. Fluticasone is a steroid that is known to dampen the release of inflammatory mediators (Robinson et al. 2009) which occurs in the lungs and is associated with anoxia (Esteban et al. 1999; Gitto et al. 2001). Salbutamol, an inhaled bronchodilator, was reported to increase partial oxygen pressure (Robertson and Bailey 2002), reduce respiratory symptoms and improve lung function (Yuksel and Greenough 1994) in preterms with RDS. In addition to this, inhaler diuretics such as furosemide alleviate non-hydrostatic pulmonary oedema (Broadstone et al. 1991; Sahni and Phelps 2011) which occurs due to loss of integrity of the alveolocapillary barrier (Gitto et al. 2001).

In conclusion, in our study, 17 of the 20 premature calves with RDS responded well to the nebuliser therapy (85%). These results indicate that nebulised salbutamol, fluticasone and furosemide are promising treatments for the restoration of lung function in premature calves with RDS. In addition to their therapeutic value, the ease of administration and low cost of these drugs are other advantages supporting their use in veterinary practice.

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