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Research Article

Effects of total parenteral nutrition and enteral fluid therapy, with or without glutamine, and crystalloid fluid therapy on the renal function of horses subjected to starvation after exploratory laparotomy

Efeitos da nutrição parenteral total e da fluidoterapia enteral associadas ou não à glutamina, e da fluidoterapia cristalóide sobre a função renal de equinos submetidos à inanição após laparotomia exploratória

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ABSTRACT

In clinical practice, variable periods of partial or total food restriction are common due to illnesses or diagnostic and/or surgical procedures, or after surgical procedures to prevent complications, such as postoperative colic. In order to assess the effect of total parenteral nutrition associated with glutamine and enteral fluid therapy, with or without glutamine, on the renal function of horses subjected to starvation after exploratory laparotomy (phase 1) and refeeding (phase 2), 16 healthy adult mixed-breed horses aged between four and 14 years and weighing on average 248.40±2.28 kg were used, divided into four experimental groups (n=4): Group I (ENTGL): enteral fluid therapy with electrolytes associated with glutamine; Group II (PARGL): total parenteral nutrition associated with glutamine; Group III (ENTFL): enteral fluid therapy with electrolytes; and Group IV (PARFL): parenteral fluid therapy. This study was divided into two phases. Phase 1 involved exploratory laparotomy and the initiation of starvation, along with the administration of treatments according to the group, while phase 2 involved refeeding the animals. There was a progressive increase in the concentration of protein in the urine, especially in the PARGL group. Glycosuria was observed in the PARGL, ENTGL, and PARFL groups. Aciduria was observed only in the PARGL group. A decrease in creatinine clearance and GGT was observed throughout the first experimental phase, considering the overall mean of the times, with heterogeneous behavior of variables within the groups.

KEYWORDS: Equine. Renal function. Fluid therapy. Refeeding. Nutritional support.

RESUMO

Na rotina clínica, são comuns períodos variáveis de restrição alimentar, parcial ou total, devido a doenças ou a realização de procedimentos diagnósticos e/ou cirúrgicos, ou após procedimentos cirúrgicos para prevenir complicações, como cólica pós-operatória. Com o objetivo de avaliar o efeito da nutrição parenteral total associada à glutamina e da fluidoterapia enteral, associada ou não à glutamina, sobre a função renal de equinos submetidos à inanição após laparotomia exploratória (fase 1) e realimentação (fase 2), foram utilizados 16 equinos adultos hígidos, sem raça definida, com idade variando entre quatro e 14 anos e peso médio de 248,40±2,28 kg, divididos em quatro grupos experimentais (n=4): grupo I (ENTGL): fluidoterapia enteral com eletrólitos associada à glutamina; grupo II (PARGL): nutrição parenteral total associada à

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glutamina; grupo III (ENTFL): fluidoterapia enteral com eletrólitos; e grupo IV (PARFL): fluidoterapia parenteral. Este estudo foi dividido em duas fases. A fase 1 consistiu na realização da laparotomia exploratória e no início da inanição, além da administração dos tratamentos, de acordo com o grupo, enquanto a fase 2 consistiu na realimentação dos animais. Houve aumento progressivo na concentração de proteína na urina, especialmente no grupo PARGL. Glicosúria foi observada nos grupos PARGL, ENTGL e PARFL. Observou-se acidúria apenas nos animais do grupo PARGL. Foi observada diminuição do *clearance* de creatinina e GGT ao longo da primeira fase experimental, quando considerado a média total dos tempos, sendo que, dentro dos grupos o comportamento das variáveis foi heterogêneo.
PALAVRAS-CHAVE: Equino. Função renal. Fluidoterapia. Realimentação. Suporte nutricional.

INTRODUCTION

Nutritional support is an auxiliary therapeutic resource in the recovery of malnourished patients or those at risk of developing malnutrition (BAEK *et al.* 2020), and should be considered for animals with an increased metabolic rate and individuals with diseases that result in an increased demand for energy (CARR 2018, MAGDESIAN & BOZORGMANESH 2018). In clinical practice, variable periods of partial or total food restriction are common, either due to certain diseases or for diagnostic and/or surgical procedures. However, the withdrawal of food for prolonged periods is not physiological, considering the feeding pattern of equines (DI FILIPPO *et al.* 2021). In natural conditions, the daily grass intake of a horse lasts between 12 to 18 hours, and when fed ad libitum, the fasting time does not exceed three hours (MAIA *et al.* 2018, MELO *et al.* 2021).

Under conditions of low food intake, some animals receive therapeutic maintenance fluid therapy, intravenous or enteral, in addition to the replenishment of daily glucose needs (LAWSON *et al.* 2021). However, current evidence indicates that these protocols may not prevent body catabolism. In this context, the use of total parenteral nutritional support would be of fundamental importance to avoid catabolism associated with a lack of food intake, thereby reducing the likelihood of post-surgical complications associated with negative energy balance (MELO *et al.* 2023).

The use of parenteral nutrition in equines has been poorly studied despite the studies carried out (MELO *et al.* 2022ab, MELO *et al.* 2023). Although parenteral nutrition is mainly described in congress proceedings, individual case reports, retrospective studies, and review articles, this therapeutic approach can be a beneficial means to ensure the proper supply of nutrients, particularly during critical illnesses or recovery from surgical procedures. However, many veterinarians hesitate to implement it not only due to the complexities of formulation, administration, and clinical monitoring but also due to potential complications and high costs (McKENZIE 2015).

This technique is still associated with various complications, including infections, catheter-related thrombosis, and metabolic disorders. In medicine, few studies have described changes in renal function in patients receiving short-term parenteral nutrition. However, a decrease in renal function, evidenced by a decrease in creatinine clearance and glomerular filtration rate, has been reported (CHALENCON *et al.* 2020). However, to the best knowledge of the authors, no studies have evaluated the renal

function of horses under parenteral nutritional support, either partial or total, up to the present date, and this was the aim of this study.

MATERIAL AND METHODS

Sixteen healthy adult mixed-breed horses of both sexes, aged between four and 14 years, with an average body weight of 248.40 ± 2.28 kg, and a body condition score of 3-4 (on a scale of 1 to 5), were divided into four groups, with four animals per group.

For the screening and selection of animals, a complete clinical examination and laboratory tests (complete blood count, biochemical profile, and fecal parasitological examination) were conducted. The animals underwent endo- and ectoparasitic treatment, initially housed in paddocks, and fed daily with commercial feed (1 kg/100 kg body weight), tifton hay (1 kg/100 kg body weight), chopped elephant grass *(Pennisetum purpureum*), water, and mineral salt ad libitum. After a 30-day adaptation period, the animals were randomly divided into four experimental groups:

ENTGL Group: Enteral fluid therapy with electrolytes (5.7g NaCl; 3.78g NaHCO3; 0.37g KCl and 10g glucose per liter of water) associated with glutamine (L-Glutamine, Ajinomoto do Brasil Indústria e Comércio de Alimentos Ltda, Laranjal Paulista/SP, Brazil). The total fluid volume administered over 24 hours was calculated at 60 ml/kg body weight as the maintenance rate. The calculated total fluid volume was divided by 12 and administered, by gravity flow, every two hours via an 11x16mm nasogastric tube. Glutamine was administered at a dose of 0.5g/kg body weight. The total calculated amount of glutamine was divided by 12 and administered every two hours diluted in enteral fluid therapy. The fluid volume to be administered, as well as the amount of glutamine, was corrected daily according to the animal's weight.

PARGL Group: Total parenteral nutrition (TPN) associated with glutamine. TPN was prepared from solutions of amino acids (Aminoven 10%, Fresenius Kabi, Barueri/SP, Brazil), lipids (Lipovenos 20%, Fresenius Kabi), and 50% glucose (Glucose 50%, Fresenius Kabi) in equal proportions (33.33% amino acids, 33.33% lipids, and 33.33% 50% glucose) to provide the daily maintenance energy requirement. Glutamine was administered at a dose of 0.5g/kg of body weight intravenously as a sterile 1.5% solution (15 g/l). The total amount of TPN, as well as the amount of glutamine to be administered, was corrected daily according to the body weight of the animal. Both solutions were administered in continuous infusion via venous access in the right external jugular vein. The administration rate (ml/h) was calculated by dividing the total volume to be infused by 24. Intravenous fluid therapy using lactated Ringer's solution was instituted as needed to complete the daily maintenance requirement of 60 ml/kg.

ENTFL Group: Enteral fluid therapy with electrolytes (5.7g NaCl; 3.78g $NaHCO_3^-$; 0.37g KCl and 10g glucose per liter of water). The total fluid volume to be administered over 24 hours was calculated at 60 ml/kg as the maintenance rate (MELO *et al.* 2010). The calculated total fluid volume was divided by 12 and administered, by gravity flow, every two hours via an 11x16mm nasogastric tube. The administered fluid volume was corrected daily according to the animal's weight.

PARFL Group: Parenteral fluid therapy. The fluid volume administered was 60 ml/kg of body weight, with half of the volume provided by lactated Ringer's solution and half by 0.9% sodium chloride solution. Glucose 50% was provided at a dose of 1.5 g/kg of body weight diluted in the saline solution. Both solutions were administered in continuous infusion via venous access in the right external jugular vein. Venous access for TPN infusion (PARGL group) and parenteral fluid therapy (PARFL group) was obtained using a double-lumen catheter (Duocath – 12F, Intra Special Catheters, Germany), coaxial 12-gauge and 20 cm in length.

This study was divided into two phases: phase 1 and phase 2. Phase 1 involved the performance of exploratory laparotomy and the initiation of starvation, along with the administration of treatments according to the group, while phase 2 involved the refeeding of the animals. During phase 1, the animals received no food or water beyond what was described for each group. In the first two days of phase 1, the TPN administered in the PARGL group provided only 50% and 75% of the energy maintenance needs, respectively, while 100% of the requirement was provided from the third day of phase 1 until its completion. In phase 2, all animals, regardless of the group, were refed with tifton hay, commercial concentrate, and water. Feeding was gradually reintroduced. On the first day, 4 kg of tifton hay were provided, divided into two meals of 2 kg each, with a 12-hour interval, and 0.5 kg of commercial concentrate. On the second day, the amount of hay was increased to 8 kilograms, provided in two meals of 4 kg each, in addition to 1 kg of commercial concentrate. From the third day onward, the amounts of food provided were equal to those during the adaptation period. Each phase had a total duration of 144 hours.

To simulate a surgical stress situation and aiming to obtain intestinal samples used in a parallel study (FERREIRA *et al.* 2022), the animals underwent two flank laparotomies, one at the beginning and another at the end of phase 1. After accessing the cavity, the standard procedure involved the exteriorization of the small intestine followed by the exteriorization of the large intestine, avoiding excessive manipulation of the loops. After collecting intestinal biopsies and performing enteric-anastomosis, the intestinal segment was returned to the abdominal cavity, and laparorrhaphy was performed (MELO *et al.* 2022b). Each performed laparotomy lasted an average of 60 minutes.

Renal function was assessed by determining the volume of urine produced over 24 hours (V24) and the serum and urinary concentrations of sodium, potassium, creatinine, GGT, and osmolality. Urine samples were collected during the 24-hour period using a collection bag. The volume of urine produced was measured every six hours and stored in a 20-liter container. Each 24-hour urine volume measurement period corresponded to a cycle of urinary clearance. In phase 1, five renal clearance cycles were evaluated, while in phase 2, two cycles were evaluated. At the end of each cycle, 15 ml urine samples were collected in falcon tubes for analysis (biochemistry and sediment microscopy).

For laboratory assays (urinary protein, glucose, creatinine, and GGT), after centrifugation, samples of the supernatant were placed in 1.5ml Eppendorf tubes and kept at -20 °C until analysis.

Reagent strips for "dipstick" urinalysis were used to assess pH, as well as the presence of blood, leukocytes, bilirubin, and ketones.

For urinary protein, glucose, creatinine, and GGT assays, a semi-automatic biochemical analyzer (Cobas Mira Plus- Roche) was used, employing commercial kits. The urinary protein assay using a commercial kit was based on the pyrogallol red principle, in a final point reaction with a wave length of 620nm. The urinary creatinine assay was performed using the Jaffé principle (alkaline picrate), using the commercial kit in a final point reaction with a wavelength of 505nm.

Urinary sediment microscopy was performed after centrifugation of the sample (2000 rpm/3min) and removal of the supernatant. For this purpose, light microscopy was used to identify the presence of epithelial cells, red blood cells, leukocytes, crystals, and cylinders (SCHOTT & ESSER 2020).

The evaluation of urinary protein excretion was performed by estimating 24-hour proteinuria using the following formula (Equation 1):

$$\textit{24-Hour Proteinuria} = \frac{\textit{Pur (mg/dl) x Vurt (ml) x 100}}{\textit{Body Weight (kg)}} \qquad \text{Eq. (1)}$$

where: *Pur: Urinary protein concentration*
Vurt: Urinary volume
Osmolality was estimated by the following formula (Equation 2):

$$\textit{Osmolality: 1.86 x } (Na^{+} + K^{+}) + \textit{(BUN/2.8) + (glucose/18) + 9} \qquad \text{Eq. (2)}$$

For the assessment of creatinine clearance (Ccr), the following formula was adopted (Equation 3):

$$\textit{Ccr (mL/min/kg)} = \frac{\textit{Cur (mg/dl) x Vurm (ml/min) x 100}}{\textit{Csr (mg/dl) x T(min)}} \qquad \text{Eq. (3)}$$

where:
Ccr: Creatinine clearance
Cur: Urinary creatinine concentration
Vurm: Urinary volume per minute
Csr: Serum creatinine concentration
T: Time

For the assessment of GGT clearance (GGTcr), the following formula was adopted (Equation 4):

$$\textit{GGTcr (mL/min/kg) = GGTur (mg/dl) x Vurm (ml/min) x 100 GGsr (mg/dl) x T(min)} \qquad \text{Eq. (4)}$$

where:
GGTcr: GGT clearance
GGTur: Urinary GGT concentration
Vurm: Urinary volume per minute
GGTsr: Serum GGT concentration
T: Time

For the assessment of fractional excretion of Na^+ and K^+, the serum and urinary concentrations of these electrolytes and creatinine were obtained from samples over a 24-hour period. The calculations were made using the formula below (Equation 5):

$$EFa = \frac{Ua\ (mEq/L) \times Csr\ (mg/dl)}{Cur\ (mg/dl)} \quad \text{Eq. (5)}$$

where:
Ua: Concentration of a specific electrolyte in the urine
Csr: Concentration of serum creatinine
Cur: Concentration of urinary creatinine

RESULTS AND DISCUSSIONS

There were no interactions or differences ($p \geq 0.05$) between the overall group means and between the overall time means in both experimental phases for plasma osmolarity values (Table 1).

Table 1. Mean ± standard error of plasma osmolality (μOsm/kg) of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

	Experimental groups				
Times	**ENTFL**	**ENTGL**	**PARFL**	**PARGL**	**Total**
Phase 1 – Starvation					
T_1	343.75 ± 44.38	297.00 ± 27.41	281.00 ± 16.70	290.75 ± 31.41	303.12 ± 15.43
T_2	309.50 ± 26.77	303.75 ± 33.44	302.50 ± 40.99	278.25 ± 24.46	298.50 ± 14.67
T_3	294.25 ± 31.54	291.75 ± 37.05	290.25 ± 45.46	275.50 ± 25.39	287.93 ± 16.04
T_4	285.50 ± 33.69	298.00 ± 36.38	287.75 ± 36.33	313.25 ± 57.06	296.12 ± 18.96
T_5	301.50 ± 35.78	301.25 ± 37.33	347.00 ± 86.92	318.75 ± 43.01	317.12 ± 25.04
T_6	297.75 ± 37.75	295.50 ± 37.65	288.75 ± 39.68	305.25 ± 48.53	296.81 ± 18.46
T_7	291.25 ± 36.33	259.33 ± 2.90	280.25 ± 35.55	305.25 ± 42.08	285.66 ± 16.35
Total	303.35 ± 12.34	293.59 ± 11.50	296.78 ± 16.34	298.14 ± 13.82	
Phase 2 – Refeeding					
T_8	265.00 ± 15.45	265.66 ± 9.93	405.75 ±102.17	276.75 ± 11.80	305.80 ± 29.70
T_9	303.25 ± 44.63	256.00 ± 4.00	313.50 ± 62.56	361.50 ± 103.87	312.06 ± 32.36
T_{10}	272.00 ± 15.49	275.66 ± 12.91	321.00 ± 66.38	276.00 ± 12.50	287.64 ± 18.74
T_{11}	275.00 ± 17.02	275.33 ± 19.37	280.00 ± 29.93	261.66 ± 6.35	273.64 ± 9.76
T_{12}	281.50 ± 20.06	274.66 ± 18.97	306.25 ± 50.25	267.00 ± 8.62	284.00 ± 14.98
T_{13}	303.00 ± 18.47	275.33 ± 19.23	291.50 ± 40.26	292.33 ± 15.38	290.61 ± 12.98
Total	282.43 ± 9.41	270.44 ± 5.51	319.66 ± 24.28	292.20 ± 20.51	

Reference value: 270 – 300 μOsmol/kg. Source: Carlson (2006). $p \geq 0.05$ – Duncan's test.

The primary contributor to plasma osmolality is Na^+, with urea, glucose, and potassium playing a smaller role in this variable. The lack of significant changes in osmolality values may be justified by its main determinant, the Na^+ ion, showing no alterations, as demonstrated by MELO *et al.* (2022a). Despite the observed increase

in glucose concentrations, particularly in the PARGL group in another study by this research group, it was not sufficient to alter osmolality values in this specific group.

The determination of plasma osmolality proved to be an important tool for assessing the hydration status of horses, highlighting the effectiveness of the fluid therapy dose used in maintaining the fluid balance of the animals. This also provided evidence that both total parenteral nutrition (NPT) and the administration of 50% glucose in the fluid therapy scheme did not alter their values, even with high rates of glucose infusion.

There was an increase in daily urine production for the PARFL and PARGL groups between T2 and T5 compared to the other groups. Regarding the average values of urine volume per kg (Table 2), a decrease was observed from the fifth cycle of renal function evaluation.

Table 2. Mean ± standard error of total daily urine volume (ml) and urine volume per kg (ml/kg) of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

	Experimental groups				
Times	**ENTFL**	**ENTGL**	**PARFL**	**PARGL**	**Total**
Total daily urine volume (ml)					
			Phase 1 – Starvation		
C_1	15910.00 ± 2433.59	12195.00 ± 1303.88	9815.50 ± 2227.89	12869.75 ± 890.40	12697.56 ± 992.00
C_2	17970.00 ± 1924.23	14073.75 ± 983.36	13137.25 ± 680.12	15942.50 ± 1313.63	15280.88 ± 756.03
C_3	18862.50 ± 2598.23	14582.50 ± 1352.21	16375.50 ± 1268.14	16825.00 ± 1474.01	16661.38 ± 878.97
C_4	10236.25 ± 1862.52	17866.67 ± 3399.06	14836.75 ± 747.61	16020.00 ± 1593.62	14531.47 ± 1122.36
C_5	6175.00 ± 1390.33	11560.00 ± 2132.53	7516.50 ± 1691.87	8140.00 ± 2589.93	8133.73 ± 1017.50
Total	13830.75 ± 1390.34	13982.50 ± 862.57	12336.30 ± 941.22	13959.45 ± 990.79	
			Phase 2 – Refeeding		
C_6	5347.50 ± 1706.44	4396.67 ± 1069.74	5630.00 ± 1297.62	4873.33 ± 775.10	5122.86 ± 909.42
C_7	3130.00 ± 1176.85	3730.00 ± 70.00	4261.00 ± 2695.13	3223.33 ± 374.97	3551.00 ± 689.73
Total	4238.75 ± 1047.08	4063.33 ± 502.06	5043.29 ± 1263.04	4048.33 ± 1834.26	
Urine volume per kilogram (ml/kg)					
			Phase 1 – Starvation		
C_1	58.75 ± 7.56^A	44.49 ± 5.16^B	39.05 ± 10.68^B	57.60 ± 3.95^A	49.97 ± 3.92
C_2	67.59 ± 2.99^A	51.18 ± 3.54^B	47.10 ± 9.67^B	71.57 ± 6.49^A	59.36 ± 3.88
C_3	44.63 ± 23.28	53.64 ± 6.10	64.88 ± 5.13	75.76 ± 6.32	59.73 ± 6.43
C_4	42.35 ± 11.27	66.78 ± 16.39	67.79 ± 5.65	71.52 ± 3.83	61.80 ± 5.25
C_5	23.77 ± 3.79	43.29 ± 9.66	33.19 ± 7.20	36.24 ± 10.18	33.51 ± 3.96
Total	47.42 ± 5.96	51.53 ± 3.70	50.40 ± 4.47	62.54 ± 4.23	
			Phase 2 – Refeeding		
C_6	19.65 ± 5.82	15.75 ± 3.05	35.67 ± 12.70	20.91 ± 15.42	23.66 ± 5.07
C_7	8.36 ± 3.35	13.53 ± 0.77	25.26 ± 7.20	15.19 ± 7.00	15.59 ± 2.92
Total	14.81 ± 4.06	14.64 ± 1.49	31.21 ± 7.61	18.05 ± 7.68	

Means followed by different uppercase letters in the row (Kruskal-Wallis test) differ (p≤0.05).

The initial moment of the decrease in urine volume per kg coincided with the start of the refeeding phase and voluntary water intake. One of the causes for this decrease in urine volume per kg may have been the low water intake observed during the refeeding phase in all groups (Table 3).

Table 3. Mean ± standard error of total daily water intake (liters) and water intake per kilogram of body weight (ml/kg) during the refeeding phase of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

Times	Experimental groups				Total
	ENTFL	ENTGL	PARFL	PARGL	
	Total daily water consumption (liters)				
T_8	6.50 ± 0.50	4.33 ± 2.33	9.75 ± 3.11	6.25 ± 1.03	6.86 ± 1.02
T_9	8.25 ± 0.62	10.00 ± 3.05	7.25 ± 1.10	10.00 ± 3.05	8.71 ± 0.91
T_{10}	8.25 ± 0.85	7.33 ± 1.45	7.00 ± 1.22	10.00 ± 5.00	8.07 ± 1.06
T_{11}	7.00 ± 1.08	10.00 ± 1.15	8.00 ± 1.22	9.00 ± 3.00	8.35 ± 0.78
T_{12}	7.00 ± 0.91	11.33 ± 3.52	7.75 ± 1.65	8.00 ± 1.15	8.35 ± 0.94
T_{13}	7.66 ± 1.20	12.00 ± 2.30	10.50 ± 3.01	8.66 ± 0.66	9.76 ± 1.09
Total	7.43 ± 0.34	9.16 ± 1.05	8.37 ± 0.79	8.52 ± 0.96	
	Water consumption per kilo (ml/kg)				
T_8	25.69 ± 1.76	16.44 ± 8.60	43.04 ± 13.98	28.76 ± 5.04	29.28 ± 4.59
T_9	32.90 ± 5.16	36.35 ± 11.08	30.69 ± 4.31	45.10 ± 10.50	35.62 ± 3.58
T_{10}	31.48 ± 1.37	26.21 ± 4.88	29.11 ± 4.29	43.13 ± 18.43	32.17 ± 4.01
T_{11}	27.17 ± 4.40	36.05 ± 4.73	33.41 ± 5.04	39.83 ± 10.20	33.57 ± 2.96
T_{12}	27.62 ± 5.05	40.80 ± 12.66	32.02 ± 6.39	36.03 ± 3.06	33.51 ± 3.43
T_{13}	30.66 ± 4.73	43.06 ± 8.78	43.47 ± 12.06	39.67 ± 0.32	39.54 ± 4.14
Total	29.19 ± 1.54	33.15 ± 3.78	35.29 ± 3.33	38.23 ± 3.54	

Regarding urine density (Table 4), the mean values remained stable during phase 1, showing an increase in the refeeding phase, probably resulting from the activation of urine concentration mechanisms. Horse urine is three to four times more concentrated than plasma (specific gravity 1030-1040), but a wide variation can be observed. Hyposthenuria was observed in samples from all animals during phase 1. This hyposthenuria may have resulted from continuous glucose supply through oral and enteral routes, specifically glycosuria. Elevated blood glucose levels exceed the renal reabsorption limit, leading to glucose being excreted in the urine. The presence of glucose in the urine can lead to the excretion of large amounts of water, as glucose drags water with it in the urine.

Table 4. Mean ± standard error of urine density of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

Times	Experimental groups				Total
	ENTFL	ENTGL	PARFL	PARGL	
	Phase 1 – Starvation				
C_1	1010.50 ± 0.95	1015.00 ± 3.69	1015.25 ± 2.80	1012.50 ± 1.89	1013.31 ± 1.24
C_2	1009.00 ± 0.57	1012.50 ± 0.95	1011.50 ± 2.87	1013.00 ± 1.91	1011.50 ± 0.90
C_3	1009.00 ± 1.29	1013.50 ± 3.77	1010.25 ± 1.93	1017.50 ± 4.11	1012.56 ± 1.59
C_4	1018.50 ± 9.87	1008.67 ± 1.76	1009.50 ± 1.25	1013.00 ± 2.38	1012.67 ± 2.67
C_5	1019.50 ± 7.32	1013.33 ± 4.37	1009.50 ± 2.06	1016.00 ± 5.35	1014.67 ± 2.54
Total	1013.30 ± 2.45	1012.78 ± 1.34	1011.20 ± 1.02	1014.40 ± 1.43	

Phase 2 - Refeeding					
C_6	1024.50 ± 2.87	1029.33 ± 2.90	1025.25 ± 1.88	1027.33 ± 8.19	1026.36 ± 1.87
C_7	1037.50 ± 1.89	1028.67 ± 4.37	1032.00 ± 4.00	1022.00 ± 5.03	1030.62 ± 2.31
Total	1031.00 ± 2.92	1029.00 ± 2.35	1028.14 ± 2.27	1024.67 ± 4.46	

Hyperglycemia directly influences both serum osmolality and urine density, playing a crucial role in the regulation of body fluids. When blood glucose concentration is elevated, serum osmolality also increases, as glucose is a solute. This means that the blood becomes more concentrated. To counteract this imbalance, the kidneys begin to filter and excrete excess glucose in the urine. However, this glucose excretion results in water loss, leading to urine dilution and consequently, a reduction in urine density.

Although average water intake values did not vary over time during refeeding, the obtained values are well below the recommended maintenance values (60 ml/kg) for horses. No apparent and specific cause was found for this low water intake in this study, but it is necessary to consider the stress resulting from maintenance in stalls to monitor the refeeding phase and even postoperative discomfort. In daily clinical practice, low water intake after abdominal laparotomies is commonly observed, which could explain the findings of this study. It has been shown that horses subjected to stress or changes in the environment may have lower water intake volumes than recommended (FREEMAN *et al.* 2021).

The results obtained in this study suggest that during the refeeding period, water intake may be lower due to the re-establishment of forage intake, a phenomenon explained by the reservoir hypothesis. The reservoir hypothesis demonstrates that dietary fiber can play a fundamental role in maintaining fluid balance and plasma volume, even in the face of low water intake, as in competition horses. Studies in ponies have shown that water can be absorbed from the gastrointestinal tract during periods of low water intake. Recently, it has been demonstrated that the role of forage in maintaining equine fluid balance is directly related to the maturation stage, with forages harvested at younger stages being more beneficial. During the refeeding period of the animals in this study, forage was offered at an early stage of maturity, providing a readily available fluid reservoir from the large intestine (MUHONEN *et al.* 2022, MUHONEN & JULLIAND 2023).

The average values of urinary osmolality remained within the reference values for the species throughout the experimental period. Regarding urinary pH (Table 5), a numerical decrease was observed during phase 1 in the PARGL group, a fact not observed in the other groups.

Under normal conditions, the pH of horse urine is alkaline. However, conditions such as prolonged starvation or metabolic disorders can result in the production of acidic urine (SCHOTT & ESSER 2020). Despite all groups being subjected to a starvation period, acidification of urine was observed only in the PARGL group. Apparently, this aciduria may be related to the metabolism of the amino acids isoleucine, valine, methionine, and threonine provided by NPT, resulting in an increase in the amount of propionate in circulation and, consequently, the development of

propionic aciduria (SBAÏ *et al.* 1994). However, the mechanism of aciduria in horses associated with NPT infusion requires further studies for confirmation.

Table 5. Mean ± standard error of urinary pH of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

	Experimental groups				
Tempos	**ENTFL**	**ENTGL**	**PARFL**	**PARGL**	**Total**
Phase 1 – Starvation					
C_1	8.50 ± 0.28	8.50 ± 0.50	7.75 ± 0.62	7.75 ± 0.47	8.12 ± 0.23
C_2	8.87 ± 0.12	8.00 ± 0.40	7.62 ± 0.37	6.75 ± 0.85	7.81 ± 0.30
C_3	8.75 ± 0.25	8.00 ± 0.57	7.37 ± 0.80	7.12 ± 0.51	7.81 ± 0.30
C_4	8.87 ± 0.12^{A}	9.00 ± 0.00^{A}	8.12 ± 0.31^{AB}	6.62 ± 0.47^{B}	8.10 ± 0.28
C_5	8.00 ± 0.40^{AB}	9.00 ± 0.00^{A}	7.12 ± 0.51^{AB}	6.75 ± 0.47^{B}	7.63 ± 0.29
Média	8.60 ± 0.12	8.44 ± 0.20	7.60 ± 0.23	7.00 ± 0.24	
Phase 2 - Refeeding					
C_6	8.50 ± 0.28	7.33 ± 0.33	7.87 ± 0.65	6.33 ± 0.88	7.60 ± 0.33
C_7	7.50 ± 0.50	8.66 ± 0.33	7.66 ± 0.33	7.33 ± 1.20	7.76 ± 0.32
Total	8.00 ± 0.32	8.00 ± 0.36	7.78 ± 0.37	6.83 ± 0.70	

Reference value: 7.00 – 9.00. Source: Carlson (2006). Means followed by different uppercase letters in the row (Kruskal-Wallis test) and lowercase letters (Friedman test) differ (p≤0.05).

Regarding creatinine and GGT clearance (Table 6), there was a decrease in their value throughout the first experimental phase when considering the total average times, but within the groups, the behavior of the variables was heterogeneous.

Table 6. Mean ± standard error of creatinine clearance and GGT of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

	Experimental groups				
Times	**ENTFL**	**ENTGL**	**PARFL**	**PARGL**	**Total**
Clearance of creatinine					
Phase 1 – Starvation					
C_1	105.95 ± 0.13	74.86 ± 29.90	63.40 ± 25.03	71.89 ± 29.20	80.07 ± 15.11
C_2	40.09 ± 16.16	116.69 ± 27.56	45.19 ± 22.45	55.15 ± 25.09	65.55 ± 13.37
C_3	18.46 ± 7.26^{B}	87.36 ± 19.43^{A}	53.40 ± 11.22^{AB}	60.25 ± 20.48^{AB}	54.87 ± 9.43
C_4	18.86 ± 9.03^{B}	114.49 ± 19.25^{A}	43.26 ± 8.09^{AB}	56.80 ± 21.52^{AB}	54.61 ± 11.11
C_5	32.13 ± 8.63^{AB}	52.14 ± 7.95^{A}	34.46 ± 5.63^{AB}	16.76 ± 6.22^{B}	32.66 ± 4.51
Total	43.10 ± 11.01	89.75 ± 10.97	47.24 ± 6.03	52.17 ± 9.70	
Phase 2 - Refeeding					
C_6	103.67 ± 38.72	48.82 ± 24.26	92.17 ± 60.48	17.56 ± 9.50	70.18 ± 21.23
C_7	41.12 ± 17.68	58.80 ± 16.33	104.78 ± 15.79	32.74 ± 26.00	59.36 ± 11.78
Total	76.86 ± 25.15	53.81 ± 13.27	97.57 ± 32.97	25.15 ± 12.84	
Clearance of GGT					
Phase 1 – Starvation					
C_1	1.45 ± 0.67	1.33 ± 0.29	1.31 ± 0.51	0.91 ± 0.21	1.25 ± 0.20
C_2	0.99 ± 0.21	1.33 ± 0.14	1.28 ± 0.70	1.19 ± 0.31	1.19 ± 0.15
C_3	2.25 ± 1.74	1.60 ± 0.65	1.08 ± 0.46	1.50 ± 0.33	1.61 ± 0.44
C_4	0.74 ± 0.09	1.43 ± 0.39	1.05 ± 0.28	1.12 ± 0.29	1.06 ± 0.13
C_5	0.50 ± 0.21	0.97 ± 0.05	1.25 ± 0.16	1.77 ± 0.81	0.99 ± 0.25
Total	1.19 ± 0.36	1.35 ± 0.16	1.06 ± 0.18	1.30 ± 0.19	

Phase 2 - Refeeding					
C_6	1.27 ± 0.72	1.55 ± 0.35	4.59 ± 2.82	14.34 ± 13.90	5.08 ± 2.98
C_7	0.31 ± 0.18	0.67 ± 0.24	2.94 ± 0.61	1.27 ± 1.07	1.30 ± 0.40
Total	0.86 ± 0.43	1.11 ± 0.27	3.88 ± 1.56	7.81 ± 6.88	

Means followed by different uppercase letters in the row (Kruskal-Wallis test) differ (p ≤ 0.05).

No interaction was identified between time and group (p≥0.05), and there was no difference between the total times (p≥0.05) in both phases and the total groups in phase 2 for fractional sodium excretion (FENa) (Table 7). A difference (p≤0.05) was identified only in the total groups in phase 1, with lower mean values being observed in the ENTGL group. Regarding fractional potassium excretion (FeK), a numerical increase was observed in the ENTFL and PARGL groups during the first phase. In the refeeding phase, a numerical decrease in mean values was observed.

Table 7. Mean ± standard error of fractional excretion of sodium (%) and potassium (%) of horses under total parenteral nutrition associated with glutamine (PARGL), fluid therapy (PARF), enteral fluid therapy without glutamine (ENTFL), and enteral fluid therapy with glutamine (ENTGL) subjected to starvation after exploratory laparotomy.

Experimental groups					
Times	**ENTFL**	**ENTGL**	**PARFL**	**PARGL**	**Total**
Fractional excretion of sodium (%)					
Phase 1 – Starvation					
C_1	2.73 ± 0.65	10.72 ± 8.74	1.45 ± 0.06	3.35 ± 1.32	7.22 ± 2.59
C_2	13.13 ± 7.68	1.92 ± 0.71	3.86 ± 0.99	9.13 ± 5.74	7.22 ± 2.59
C_3	6.06 ± 1.51	2.37 ± 1.08	3.54 ± 0.88	6.13 ± 3.96	4.52 ± 1.08
C_4	16.91 ± 9.28	2.03 ± 0.80	4.45 ± 0.84	9.67 ± 7.16	8.68 ± 3.19
C_5	3.16 ± 0.96^{AB}	2.34 ± 0.32^{B}	2.48 ± 0.39^{B}	10.73 ± 7.02^{A}	4.83 ± 1.94
Total	8.40 ± 2.52	4.06 ± 1.95	3.21 ± 0.38	7.80 ± 2.27	
Phase 2 - Refeeding					
C_6	0.83 ± 0.16	3.70 ± 3.37	2.28 ± 1.11	7.45 ± 5.20	3.28 ± 1.34
C_7	0.56 ± 0.06	0.88 ± 0.24	0.60 ± 0.08	2.54 ± 1.90	1.14 ± 0.47
Total	0.71 ± 0.10	2.29 ± 1.64	1.56 ± 0.68	4.99 ± 2.71	
Fractional excretion of potassium (%)					
Phase 1 – Starvation					
C_1	9.12 ± 1.81	61.64 ± 52.86	5.39 ± 1.02	11.80 ± 3.91	23.09 ± 14.13
C_2	55.97 ± 35.86	10.93 ± 3.69	18.46 ± 8.18	53.19 ± 34.53	35.72 ± 13.18
C_3	25.89 ± 8.65	9.32 ± 4.68	18.22 ± 4.22	67.95 ± 60.68	30.35 ± 14.95
C_4	88.57 ± 59.46	13.26 ± 5.99	19.49 ± 5.21	53.30 ± 43.63	45.68 ± 19.43
C_5	12.49 ± 5.18	13.35 ± 1.85	7.98 ± 1.46	68.91 ± 54.16	26.50 ± 14.71
Total	38.41 ± 14.25	22.63 ± 11.72	14.13 ± 2.28	51.03 ± 18.16	
Phase 2 - Refeeding					
C_6	4.51 ± 1.01	16.41 ± 12.32	9.40 ± 4.42	46.76 ± 38.13	17.51 ± 8.57
C_7	3.07 ± 0.80	5.29 ± 1.74	3.48 ± 0.68	8.52 ± 4.21	5.09 ± 1.19
Total	3.89 ± 0.68	10.85 ± 6.09	6.86 ± 2.66	27.64 ± 19.17	

Means followed by different uppercase letters in the row (Kruskal-Wallis test) differ (p≤ 0.05).

The values of fractional sodium excretion (FENa) remained above the reference limit throughout the experimental period, except for values within the normal range in the ENTFL group during the refeeding phase and in the seventh clearance cycle in the

ENTGL and PARFL groups. Despite the numerical decrease in FENa values in the PARGL group, the values remained above the reference limits for the species.

Elevation of FENa values indicates a scenario of acute renal injury due to the loss of the ability to reabsorb electrolytes properly (SCHOTT & ESSER 2020). The presence of FENa values above the reference range for the species at the end of the first clearance cycle was not expected, as the animals were clinically normal. However, there may have been an effect of the sedation protocol used in this variable. The response found in the PARGL group during the first phase may indicate renal impairment due to the accumulation of lipids in the renal glomerulus as a result of intravenous lipid administration. Interestingly, once NPT was discontinued, a numerical decrease in FENa values was observed in the group.

Regarding urine protein concentration (Table 8), a progressive numerical increase was observed in the PARGL group. In relation to 24-hour proteinuria (Table 8), a numerical increase was observed in the PARGL group.

Table 8. Mean ± standard error of urine protein concentration* (g/dl) and daily proteinuria (mg/ml/kg) of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

			Experimental groups		
Times	**ENTFL**	**ENTGL**	**PARFL**	**PARGL**	**Total**
			Urine protein concentration* (g/dl)		
			Phase 1 – Starvation		
C_1	10.57 ± 6.15	0.00 ± 0.00	31.73 ± 30.46	0.55 ± 0.55	10.71 ± 7.70
C_2	0.95 ± 0.95	37.49 ± 32.57	24.52 ± 24.52	12.46 ± 8.61	18.85 ± 9.96
C_3	0.00 ± 0.00	2.40 ± 2.40	13.94 ± 13.94	42.30 ± 25.03	14.66 ± 7.75
C_4	34.13 ± 24.02	4.44 ± 4.44	0.00 ± 0.00	23.55 ± 13.74	16.27 ± 7.64
C_5	0.96 ± 0.96	0.00 ± 0.00	0.00 ± 0.00	42.30 ± 27.11	12.36 ± 8.72
Total	9.32 ± 5.32	9.60 ± 7.44	14.77 ± 8.33	24.23 ± 8.09	
			Phase 2 - Refeeding		
C_6	52.88 ± 39.53	11.53 ± 11.53	77.93 ± 57.72	204.38 ± 60.10	83.64 ± 28.17
C_7	83.65 ± 44.41	46.36 ± 43.51	113.70 ± 54.84	78.91 ± 32.67	80.88 ± 20.62
Total	68.26 ± 28.13	28.95 ± 21.58	93.26 ± 37.86	141.65 ± 41.50	
			Daily proteinuria (mg/ml/kg)		
			Phase 1 – Starvation		
C_1	10.57 ± 6.15	0.00 ± 0.00	4470.50 ± 4316.04	64.40 ± 64.40	1556.79 ± 1102.39
C_2	0.95 ± 0.95	4886.58 ± 4150.57	2942.40 ± 2942.40	2206.19 ± 1671.39	2554.46 ± 1274.57
C_3	0.00 ± 0.00	260.19 ± 260.19	2133.20 ± 2133.20	6131.03 ± 3629.02	2131.10 ± 1135.82
C_4	34.13 ± 24.02	1077.51 ± 1077.51	0.00 ± 0.00	4056.86 ± 2483.31	2183.75 ± 904.49
C_5	0.96 ± 0.96	0.00 ± 0.00	0.00 ± 0.00	1949.93 ± 1149.16	572.24 ± 381.69
Total	1050.39 ± 509.02	1323.31 ± 960.41	2009.70 ± 1131.78	2881.68 ± 981.75	
			Phase 2 - Refeeding		
C_6	3663.30 ± 3575.38	484.54 ± 484.54	9669.05 ± 9232.41	6001.50 ± 3129.38	5199.11 ± 2767.93
C_7	1959.85 ± 1335.62	1740.48 ± 1630.95	5365.11 ± 2969.57	1817.61 ± 461.54	2662.23 ± 877.54
Total	2811.57 ± 1795.88	1112.51 ± 811.06	7824.51 ± 5135.11	3909.56 ± 1696.01	

*Pirogalol method

Approximately 200 different proteins (derived from both plasma and the urinary tract itself) may be present in urine. Proteins with a molecular weight below 60 kDa are

freely filtered by the glomeruli and quickly reabsorbed in the proximal tubules. Thus, conditions that increase the amount of proteins in the glomerular filtrate or decrease tubular reabsorption lead to proteinuria, in addition to the damage that can occur along the urinary tract (CARLSON 2006). Several studies in humans have demonstrated the occurrence of elevated urinary protein excretion and consequent proteinuria in hyperlipidemic patients (O'DONNELL 2001), and a high correlation between triglyceride concentration and VLDL with the magnitude of proteinuria in women (LIMA *et al.* 2011).

It is believed that hypertriglyceridemia contributes to the onset of renal injury by glomerular accumulation of lipids, particularly in the mesangium. Compared to companion animals, horses have a low incidence of protein-losing nephropathy. However, variable degrees of proteinuria during renal insult are not uncommon. Inflammatory changes in distant foci of the urinary tract can result in proteinuria in horses. Thus, the numerical increase in proteinuria observed in all groups in phase 2 may have resulted from the inflammatory stimulus of laparotomy and intestinal manipulation. These data corroborate with the results of AROSALO (2007), who observed an increase in proteinuria in horses in the postoperative period of abdominal laparotomy.

CARLSON (2006) warns that proteinuria should be analyzed in relation to other findings of urinalysis. Protein presence in the absence of leukocytes, red blood cells, bacteria, or casts suggests glomerular protein loss. The higher protein values in the PARGL group suggest the accumulation of lipids in the renal glomerulus due to intravenous lipid administration, resulting in glomerular injury, as discussed earlier.

During starvation, a difference between groups for urinary glucose values (Table 9) was observed from the second cycle of urinary clearance, with higher values being observed in the PARGL group. In the refeeding phase, glycosuria was not identified in samples from animals in any of the groups.

Table 9. Mean ± standard error of urinary glucose concentration (mg/dl) of horses under total parenteral nutrition associated with glutamine (PARGL), enteral fluid therapy with (ENTGL) or without glutamine (ENTFL), and fluid therapy (PARF) subjected to starvation after exploratory laparotomy.

	Experimental groups				
Times	**ENTFL**	**ENTGL**	**PARFL**	**PARGL**	**Total**
Phase 1 – Starvation					
C_1	0.00 ± 0.00^A	25.00 ± 50.00^A	62.50 ± 125.00^A	625.00 ± 946.48^A	178.12 ± 504.30
C_2	0.00 ± 0.00^B	0.00 ± 0.00^B	0.00 ± 0.00^B	1062.50 ± 718.07^A	265.62 ± 573.50
C_3	0.00 ± 0.00^B	0.00 ± 0.00^B	0.00 ± 0.00^B	2000.00 ± 0.00^A	500.00 ± 894.42
C_4	0.00 ± 0.00^B	0.00 ± 0.00^B	0.00 ± 0.00^B	1750.00 ± 500.00^A	466.66 ± 833.80
C_5	0.00 ± 0.00^B	0.00 ± 0.00^B	25.00 ± 50.00^B	937.50 ± 773.92^A	256.66 ± 556.41
Total	0.00 ± 0.00				
Phase 2 - Refeeding					
C_6	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
C_7	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Total	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

Means followed by different uppercase letters in the row (Kruskal-Wallis test) differ ($p \leq 0.05$).

Glucose is not found in the urine of large animals unless blood concentration increases above the renal reabsorption threshold, believed to be between 160 to 180 mg/dl in the equine species, or unless significant tubular lesions occur. Glycosuria is a constant finding in cases of hyperglycemia resulting from excessive glucose administration. In this case, its occurrence in the PARGL group is related to the persistence of a hyperglycemic state induced by NPT administration.

The identification of glycosuria in the ENTGL group was not expected, as hyperglycemia was not observed in this group in another study by this group of researchers. Despite the identification of hyperglycemia in the PARFL group at times T3, T4, and T5, glycosuria in the first cycle was not expected. It is likely that the individual response of one of the animals in the groups influenced this response and elevated the mean values, or there may have been proximal tubular injury.

Although hyperglycemia is one of the main causes of glycosuria, DIVERS & VAN METRE (2006) caution that glycosuria may occur in animals with hyperammonemia; however, this cause of glycosuria could not be evaluated in this study, since blood ammonia concentration was not determined. Still, it may partially explain the occurrence of glycosuria in the first cycle of the ENTGL group.

CONCLUSION

The renal function response in horses subjected to starvation and nutritional support postoperatively varied depending on the treatment protocols. Horses receiving total parenteral nutrition (NPT) with glucose and lipids (PARGL group) exhibited more pronounced alterations, such as aciduria, proteinuria, and glycosuria, indicating possible renal stress or dysfunction. These findings suggest that NPT, although valuable in the management of convalescent horses during critical care or post-surgical recovery, may pose risks to renal function, particularly when high rates of glucose and lipids are administered.

In horses with pre-existing renal compromise, the safety of NPT becomes even more critical. Renal dysfunction can impair the excretion of the metabolic byproducts of NPT, including excess glucose, lipids, and nitrogenous waste from amino acids, leading to an accumulation of these substances and further exacerbating renal injury. The infusion of lipids, for instance, has been associated with lipid accumulation in renal glomeruli, contributing to glomerular damage and proteinuria. Moreover, hyperglycemia induced by high glucose infusion rates can lead to osmotic diuresis and further renal stress, particularly in animals with already impaired renal filtration capacity.

Given these potential risks, the use of NPT in horses with compromised renal function should be thoroughly evaluated, with special attention to the balance of nutrient infusions and the monitoring of renal markers such as fractional sodium excretion (FENa), urine protein levels, and creatinine clearance. Adjustments in the composition of NPT, such as reducing lipid and glucose content and considering alternative energy sources, may be necessary to minimize the burden on the kidneys. Careful titration of nutrient delivery and frequent renal monitoring are essential in such cases to prevent exacerbation of renal damage.

As an alternative, partial parenteral nutrition (PPN) offers a less aggressive approach, delivering fewer calories and nutrients via the intravenous route while still supporting recovery. Studies in both human and veterinary medicine have shown that PPN can adequately support patients without the higher risks of metabolic complications, such as hyperglycemia and lipid overload, often seen with NPT. By offering a combination of enteral nutrition with partial parenteral supplementation, PPN reduces the renal burden and may present a safer option, particularly in equines with pre-existing renal concerns or those at risk of developing renal complications due to prolonged starvation or surgical stress.

Therefore, future studies should focus on optimizing both NPT and PPN protocols in horses, exploring the ideal nutrient proportions, energy delivery methods, and infusion volumes. Special emphasis should be placed on evaluating their effects on renal function, particularly in horses with compromised renal capacity, to ensure both the safety and the effectiveness of nutritional support in equine clinical practice.

NOTES

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, and formal analysis**, Melo UP, and Palhares MS**; software and validation**, Melo UP, and Palhares MS;** investigation**, Melo UP, Palhares MS, Leme FOP, Ferreira C**, **Gheller VA**, and **Maranhão RPA**; resources and data curation**, Melo UP, and Palhares MS**; writing-original draft preparation**, Melo UP**; writing-review and editing**, Melo UP, Leme FOP, and Palhares MS**; visualization**, Melo UP, Palhares MS, Leme FOP, Ferreira C**, **Gheller VA**, and **Maranhão RPA**; supervision, **Melo UP, and Palhares MS**; project administration, **Palhares MS**; funding acquisition, **Palhares MS**. All authors have read and agreed to the published version of the manuscript.

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INSTITUTIONAL REVIEW BOARD STATEMENT

This study was approved by the Animal Experimentation Ethics Committee (CETEA/UFMG) under number 34/2008.

INFORMED CONSENT STATEMENT

Not applicable because this study did not involve humans.

DATA AVAILABILITY STATEMENT

The data can be made available under request.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in the preparation, execution, and dissemination of the results of this study.

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