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Evaluation of intermittent hemodialysis therapy in the bypass mode in dogs with chronic kidney disease in uremic crisis

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Abstract

Background This study aimed to assess the safety of intermittent hemodialysis via the bypass mode in dogs with chronic kidney disease during uremic crisis.

Results Fourteen dogs with chronic kidney disease in uremic crisis were selected. The dogs were allocated into two experimental groups: intermittent hemodialysis without bypass mode (IHD group without bypass) and intermittent hemodialysis with bypass mode (IHD group with bypass). Data were collected during the first dialysis session at 10 min pre-session (M0), 30 min (M1), 60 min (M2), 120 min (M3), 180 min (M4), and 240 min (M5) after the session began and 10 min post-session (M6). An increase in rectal temperature was observed at certain moments in both groups. The hemogram revealed a decrease in red blood cells, total protein, and platelets in both groups, whereas hemoglobin and hematocrit decreased at M6 only in the IHD group with bypass. Urea, creatinine, and phosphorus were reduced at M6 in both groups. An increase in blood pH, sodium bicarbonate, and excess base at M6 (10 min post-session) was observed in both groups. The IHD group with bypass exhibited a significantly lower body weight. No significant differences were observed in session time or final URR between the groups.

Conclusions The results of this study support the hypothesis that IHD with the bypass mode is safe and effective in CKD dogs with uremic crisis. This approach minimizes complications such as dialysis disequilibrium syndrome (DDS) while not causing hemodynamic or laboratory impairments under the executed conditions.

Keywords Bypass, F4 filters, Intermittent Hemodialysis, Kidney, Safety

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Background

Chronic kidney disease (CKD) is characterized by specific kidney function laboratory alterations [1] and/or structural changes detected through ultrasonographic examination [2]. CKD staging and substaging follow the guidelines proposed by the International Renal Interest Society [3]. Typically, CKD animals remain stable and then may experience a marked reduction in kidney function, leading to uremic crisis, a serious condition necessitating hospitalization and high-cost treatments, including renal replacement therapies (RRTs), such as dialysis [4].

The use of RRTs in veterinary medicine has been steadily increasing, indicating that RRT is an advanced treatment modality for animals with CKD and acute kidney injury [5–7]. Cases of acute kidney injury, electrolyte imbalances, severe and progressive azotemia, unresponsive fluid overload to clinical treatment, and difficulty in maintaining life quality in stage IV CKD animals are common indications for RRTs [5, 8–10]. For all animals, dialysis prescription must be adapted to individual needs, such as body weight; the degree of azotemia; the presence of comorbidities; and whether it is the first, second, or subsequent session; as such, session intensity, duration, and frequency are adjusted [6].

In cases of severe uremia or in small-sized animals, or even in patients where the final blood flow (Qb) becomes limited, especially in the first dialysis session, when the risk of disequilibrium syndrome is greater, most platforms cannot precisely provide the required flow [9]. Increasing the Qb while decreasing the session time poses a risk to the patient's life, causing neurological signs such as nystagmus and tremors, which evolve into dialysis disequilibrium syndrome (DDS) [9, 11]. An alternative approach involves the alternation between active dialysis moments and bypass mode moments (brief interruption of dialysate flow), during which effective exchanges between blood and dialysate do not occur [6, 11]. Therefore, the purpose of this study was to evaluate the safety and efficiency of the intermittent hemodialysis (IHD) modality using the bypass mode in CKD dogs in uremic crisis. Thus, we hypothesized that IHD with the bypass mode is as safe as IHD without the bypass mode and does not cause significant hemodynamic or laboratory alterations. This evaluation was based on laboratory tests and clinical parameters of the animals subjected to this modality.

Table 1 Values of body weight, session time, and final URR in the IHD group without bypass and the IHD group with bypass

Variable	IHD without bypass	IHD with bypass	*P* value
Body weight (kg)	28.01 ± 3.30	12.02 ± 0.9734	0.0006
Session time (minutes)	257.1 ± 27.66	265.7 ± 23.08	0.8160
Final URR	0.57 ± 0.03	0.48 ± 0.04	0.1047

The values are presented as the means ± standard errors of the means. Statistical significance was considered for $P < 0.05$

Based on the urea values of the animals in the study (ranging from 400 to 700 mg/dL), the target URR for the first session was set to a maximum of 50%, in accordance with the recommendation by Cowgill [9]

IHD group without bypass = dogs with CKD in uremic crisis undergoing intermittent hemodialysis without bypass; IHD group with bypass = dogs with CKD in uremic crisis undergoing intermittent hemodialysis with bypass

Results

A total of 14 dogs were included in the study. The IHD group without bypass consisted of seven dogs (five males and two females), with a mean age of 5.4 ± 2.8 years. The dogs were composed of four mixed-breed dogs, one Labrador Retriever, one Dogo Argentino, and one American Pit Bull Terrier. The IHD group with bypass also included seven dogs (five males and two females), with a mean age of 5.3 ± 4.5 years, and was composed of four mixed-breed dogs, one Rottweiler, one Bull Terrier, and one Chow-chow.

Data related to body weight (kg), time of the session (minutes), and final URR are presented below (Table 1).

The IHD without bypass group presented a mean Qb of 63 ± 6 mL/min at M1, M2, and M3. The IHD with bypass group presented a mean Qb of 63 ± 6 mL/min at M1 and M2 and a mean of 66 ± 6 mL/min at M3. No statistical differences in these values were observed between the groups ($p > 0.05$). The group without bypass had an average of 2.25 mL/kg/min, whereas the bypass group had an average of 5.5 mL/kg/min.

In the IHD with bypass group, within an hour, each one of the three moments was composed of 15.1 ± 1.0 min in bypass and 4.9 ± 1.0 min in dialysis.

Clinical data assessed through variables such as heart rate, respiratory rate, and SBP did not significantly differ when groups, moments, or their interactions were compared. Only rectal temperature (°C) changed, with the IHD without bypass exhibiting higher temperature (37.7 °C) at M6 than at M1 (37.1 °C) ($P = 0.0149$). The IHD group with bypass presented a lower temperature (36.9 °C) at M2 than at M0 (37.6 °C) ($P = 0.0084$) and an increase (37.8 °C) at M6 compared with M1 (37.1 °C) ($P = 0.0186$) and M2 (36.9 °C) ($P = 0.0027$).

The urea concentrations were reduced at M6 in both groups ($P < 0.0001$), the creatinine concentrations decreased at M6 in both the IHD group with bypass ($P = 0.0031$) and the IHD group without bypass ($P < 0.0001$), whereas the phosphorus concentrations decreased at M6 in both IHD group without bypass ($P = 0.0014$) and IHD with bypass ($P = 0.017$) groups. The albumin values did not differ across any of the comparisons (Table 2).

The blood pH increased at M6 compared with M0 in both IHD group without bypass ($P = 0.0313$) and IHD with bypass group ($P = 0.0083$). Sodium bicarbonate increased at M6 compared with M0 in both IHD group

Table 2 Values for laboratory variables studied in dogs undergoing IHD without bypass and IHD with bypass at M0 and M6

Parameters	Reference interval	IHD without bypass			IHD with bypass			Between treatments	
		M0	M6	*P* value M0-M6	M0	M6	*P* value M0-M6	*P* value M0-M0	*P* value M6-M6
Urea (mg/dL)	21.4-59.92	492.7 ± 42.91	208.8 ± 25.19	< 0.0001	480.3 ± 17.6	248.3 ± 24	< 0.0001	0.794	0.279
Creatinine (mg/dL)	0.5–1.5	11.15 ± 2.19	5.046 ± 1.45	0.003	8.57 ± 0.75	4.9 ± 0.53	< 0.0001	0.289	0.926
Phosphorus (mg/dL)	2.6–6.2	15.97 ± 2.05	5.94 ± 0.86	0.001	14.53 ± 2.28	8.21 ± 0.63	0.0171	0.648	0.065
Albumin (g/dL)	2.6–3.3	2.4 ± 0.1	2.3 ± 0.1	0.289	2.4 ± 0.2	2.1 ± 0.1	0.0625	0.959	0.807
Red blood cells (10^6/µL)	5.5–8.5	**3.91 (3.15 – 17.55)**	**3.39 (3.13 – 4.02)**	0.187	4.67 ± 0.59	3.817 ± 0.50	0.001	0.588	0.661
Hemoglobin (g/dL)	12–18	**8.10 (7.47–12.1)**	**8.00 (7.25–11.4)**	0.312	10.59 ± 1.03	8.41 ± 0.76	0.004	0.804	0.667
Hematocrit %	37–55	27 ± 2.23	26.29 ± 2.29	0.355	33 ± 3.37	26.29 ± 2.49	0.013	0.164	> 0.999
MCV (fL)	60–77	65.6 ± 2.64	68.2 ± 2.1	> 0.999	**72.6 (64.6–72.8)**	**67.8 (67–72.3)**	0.068	0.240	0.662
MCHC (%)	31–36	33.7 ± 0.7	33.2 ± 0.5	0.427	33 ± 0.4	32.1 ± 0.4	0.131	0.495	0.136
Total protein (g/dL)	6–8	7.77 ± 0.30	7.22 ± 0.211	0.025	7.514 ± 0.41	6.086 ± 0.30	0.001	0.625	0.009
Platelets (10^3/µL)	160–430	158.5 ± 22.49	92.82 ± 23.04	0.001	261.6 ± 47.39	141.1 ± 28.02	0.017	0.112	0.211
pH	7.33–7.45	**7.30 (7.25–7.36)**	**7.42 (7.37–7.45)**	0.031	7.29 ± 0.03	7.36 ± 0.02	0.008	0.301	0.101
HCO_3^- (mmol/L)	19–26	15.43 ± 1.30	20.27 ± 1.25	0.012	16.29 ± 1.30	20.26 ± 0.87	0.001	0.858	0.995
BE (mmol/L)	+5 to -5	-10.22 ± 1.59	-3.43 ± 1.23	0.0060	-9.071 ± 1.66	-4.114 ± 1.90	0.0009	0.790	0.686
Potassium (mmol/L)	3.5–5.8	3.86 ± 0.17	3.44 ± 0.1	0.064	**3.64 (3.48–3.98)**	**3.59 (3.32–3.84)**	0.687	0.628	0.427
Sodium (mmol/L)	140–155	149 ± 5.1	151.3 ± 2.1[A]	0.580	161.9 ± 5.2	153.3 ± 3.1	0.580	0.106	0.589

The results are presented for comparisons between moments (*P* value M0-M6) and between treatments (*P* value M0-M0 and *P* value M6-M6)

The values in bold are expressed as medians and interquartile ranges (25–75%). Other data are presented as the means ± standard errors of the means. Statistical significance was considered for $P < 0.05$

IHD group without bypass = dogs with CKD in uremic crisis undergoing intermittent hemodialysis without bypass; IHD group with bypass = dogs with CKD in uremic crisis undergoing intermittent hemodialysis with bypass; MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; HCO_3^- = bicarbonate; BE = base excess

without bypass ($P = 0.0120$) and IHD group with bypass ($P = 0.0010$). BE increased at M6 compared with M0 in both IHD group without bypass ($P = 0.0060$) and IHD group with bypass ($P = 0.0009$). The sodium and potassium values did not differ between the groups and moments evaluated (Table 2).

Red blood cell count ($P = 0.0014$), hemoglobin ($P = 0.0049$), and hematocrit ($P = 0.0130$) were lower at M6 than at M0 only in the IHD group with bypass. The mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) did not differ among the comparisons (Table 2).

The total protein content decreased at M6 in both IHD group without bypass ($P = 0.0254$) and IHD group with bypass ($P = 0.0017$). The number of platelets decreased at M6 in both IHD group without bypass ($P = 0.0010$) and IHD group with bypass ($P = 0.0178$). The IHD group with bypass also presented lower values at M6 than did the IHD group without bypass ($P = 0.0099$) (Table 2).

The total leukocyte, segmented, and lymphocyte counts did not differ among the comparisons. At M0, monocyte levels in the IHD group with bypass (0.985 ± 0.230) were significantly greater than those in the IHD group without bypass (0.328 ± 0.064) ($P = 0.0177$).

The activated clotting time (ACT) of the IHD group without bypass was greater (321.5 s) than that of the IHD group with bypass (266.8 s) ($P = 0.028$). Descriptive values of the means and standard errors of the means for the ACT, heparin, and iCa values are presented in the supplementary material.

Discussion

This study successfully established, for the first time, a dialytic process using Fresenius F4 filters (Fresenius Medical Care®) with the bypass method in dogs with CKD. The need for the development of this technique arose from the absence of standardized usage of this type of hemodialyzer.

Frequently, smaller patients and/or severely uremic patients are unable to undergo intermittent hemodialysis because of the lack of precise and safe provision of lower Qb extracorporeal renal replacement therapy platforms (machines). In such cases, the bypass technique serves as an option [6, 11].

Cowgill [9] reported that the final Qb is directly influenced by body weight, the programmed session time, and the severity of azotemia. Hence, it is expected that animals with higher body weights will have a greater Qb than will smaller animals. The purpose of the bypass technique is to provide safe treatments, especially for animals with lower body weights or severe azotemia. As proposed, the bypass technique demonstrated similarity to the technique without bypass, as it provided comparable final Qb and Qb in mL/kg while maintaining vital parameters, even with variations in the animals' body weight. These statements demonstrate that the bypass technique employed in this study was safe.

As observed in our results, even with variations in body size between the groups and the application of different hemodialysis techniques (without and with bypass), the vital parameters remained stable, so that, if there is any possible influence of these variables, they do not appear to have a significant effect on the outcome. Furthermore, it is important to emphasize that the stability of the vital signs observed in this study, especially considering the low-weight animals undergoing hemodialysis, may have been achieved precisely by the use of the bypass mode, as this approach provides greater safety to the procedure. Considering the severity of the disease, it is expected that more severe conditions would lead to greater instability of the parameters; however, it is worth noting that the animals included in the study, although in uremic crisis, were excluded if any instability, especially hemodynamic, was present at the time of the initial evaluation, which may have contributed to the maintenance of result stability. Another important point concerns normality values. This is because, even if there were significant differences in vital parameters between the groups, it would be more important to observe whether the values were still within the reference range for the species, as this would be the most clinically relevant information for interpretation. Finally, although it is possible to apply our results to a broader population of dogs with CKD, future studies, capable of evaluating a larger number of animals, could add valuable information to this issue.

The most effective way to evaluate session efficacy is through the assessment of the final urea reduction ratio (URR), as suggested by Dufayet and Cowgill [6]. Similar final URR results in both groups indicate that the bypass modality used was effective in controlling blood purification and minimizing complications such as DDS.

The DDS encompasses a range of neurological clinical signs that can occur during or after dialysis [12] and result from rapid changes in serum sodium, urea, or bicarbonate concentrations, leading to cerebral edema and subsequent neurological manifestations [8]. When factors such as sodium stability, achievement of final URR, and the absence of neurological signs hours after the session are aligned, it suggests that the dialytic prescription was safely adjusted [11].

In addition to DDS, complications such as issues with vascular access, including thrombosis, failure to provide adequate Qb, and less commonly bleeding and infections [8], may occur. In this study, all animals were daily monitored during catheter cleaning, and none showed local signs of infection related to the catheter (hyperemia, pain, swelling, accumulation of blood-tinged or purulent secretion, or foul odor at the catheter exit), nor systemic

signs of infection, such as increased body temperature. Complications related to bleeding and/or thrombus formation were monitored in all animals through visualization of the catheter, the color of the blood in the arterial and venous lines, inspection of the appearance of the dialyzer at the end of the dialysis session, and monitoring of theVP and TMP provided by the hemodialysis platform [13].

Although slightly above the values recommended in the literature in both groups [8], the ACT value in the DIC group with bypass remained closer to the indicated range, and no animal, in either group, exhibited hemorrhagic complications [14]. It is worth noting that the baseline TCA value may have also influenced the observed results, as it can be altered by the pre-existing clinical condition, including the patient's inflammatory state [15]. An accepted alternative for assessing anticoagulation during hemodialysis is an increase of 140–180% in the TCA compared to the baseline value [8]. In this context, both groups presented average TCA values within the acceptable limits at most of the evaluation points, which may explain the absence of hemostatic complications. However, since the assessment of microbleeds is challenging and primarily involves brain tissue [16], this possibility was not investigated in depth and cannot be completely ruled out. Nevertheless, no neurological signs were observed.

Blood loss to the extracorporeal circuit is expected [5, 11, 16] and may have been accentuated in the IHD group with bypass due to the greater volume of blood passing through the dialyzer than in the group without bypass.

Although blood loss to the circuit occurs in both groups as an intrinsic part of the procedure, in patients undergoing the bypass mode, the impact of this blood loss, proportionally to the smaller total blood volume due to body weight, reflects greater clinical importance in this group, and the potential cumulative effects of this blood loss could increase the likelihood of the need for a blood transfusion more rapidly compared to the group without bypass. However, it is important to emphasize that the reduction of these variables observed in the bypass group is likely more related to the volemia of the patient, as described earlier, rather than to the bypass procedure itself, as the possibility of increased Qb during the session due to this approach minimizes the risks of clot formation, which could further impact this result.

Regarding the results of the laboratory evaluations, it is known that one of the main effects of hemodialysis is its ability to substitute renal excretion function. Thus, the reduction of small solutes such as urea, creatinine, and phosphorus is achieved through this technique [8]. Our results showed that the use of the bypass mode did not impact the efficiency of hemodialysis in this aspect. However, it is important to emphasize that this therapeutic result is generally temporary, regardless of the technique used; that is, these dialyzable solutes may increase during the intervals between dialysis treatments [8], so sustained reduction of these compounds in the long term is entirely dependent on the patient's residual renal function after stabilization of the condition [17]. However, once the reduction of potentially harmful metabolites is achieved through hemodialysis, this improves the overall organic condition of the patient and enhances the possibility of stabilization and responses to the underlying treatment [8].

The impact of hemodialysis on the patient's acid-base status is also expected and was observed in this study. In both groups, bicarbonate levels increased significantly at the end of the procedure, clinically impacting the correction of the metabolic acidosis present in these animals. The diffusion of bicarbonate from the dialysate to the blood explains this result [5, 9]. Similarly, as observed in both groups evaluated, electrolytes carefully contained in the dialysate and adjusted during prescription allow for eventual corrections or electrolyte stabilization of the patient according to the concentration between the compartments.

HDI is a treatment used to support patients with CKD, and in veterinary medicine, it is used in patients with CKD in uremic crisis. The long-term laboratory and clinical stability of the patient is directly dependent on the underlying cause of the exacerbation and its proper treatment, the time until the institution of appropriate clinical therapy, residual renal function, associated complications, and early referral for dialysis techniques. However, in the study by Picelli de Azevedo et al. [18], it is already demonstrated that despite the mortality rate, HDI was able to promote clinical and laboratory improvement in patients during the uremic crisis, which ensured an improvement in the quality of life of these animals.

Finally, occurring once again in both groups and highlighting the congruence between the two techniques, the significant reduction in total protein observed after the hemodialysis procedure may be linked to the passage of small transmembrane proteins [19], since there was no significant reduction in albumin. Furthermore, even with the observed reduction, total protein values remained within the reference range for the species, not representing a clinically significant decrease.

A limitation of this study is the lack of standardization in the filters used for the group without bypass. Additionally, future studies with larger sample sizes and a longer follow-up time for these animals, along with life quality's assessments, may provide a more detailed understanding of the long-term implications of the technique.

Conclusion

The results of this study support the hypothesis that intermittent hemodialysis via the bypass mode is safe and effective in CKD dogs with uremic crisis. This approach minimizes complications such as DDS while not causing hemodynamic or laboratory impairments under the executed conditions.

Methods

This study was approved by the ethics committee (Comitê de Ética no Uso de Animais - CEUA) of the Faculty of Veterinary Medicine and Animal Science, UNESP (protocol number 0084/2021).

Animal selection

The animals included in this study were selected during a visit to the Veterinary Nephrology and Urology Service at the Small Animal Medical Clinic of the Veterinary Hospital of the Faculty of Veterinary Medicine and Animal Science, UNESP in Botucatu, São Paulo.

Fourteen dogs, regardless of sex, age, or breed, were selected for this study. The animals were diagnosed with CKD on the basis of abdominal ultrasonography findings [2] and in accordance with the guidelines of the International Renal Interest Society [3]. The dogs experienced uremic crisis and were refractory to previous clinical treatments. Uremic crisis was identified by clinical signs such as vomiting, diarrhea, loss of appetite, depression, lethargy, and weakness resulting from biochemical and physiological alterations due to declining kidney function.

The exclusion criteria included animals presenting with clinical conditions consistent with shock, clinical instability with signs of heart failure, severe pulmonary alterations, severe dehydration, hypotension (systolic blood pressure (SBP) < 60 mmHg), hypothermia, a significantly altered mental state, animals at risk of bleeding, or animals with hematocrit levels below 18%.

The animals were allocated into two experimental groups. The intermittent hemodialysis (IHD) group without bypass consisted of seven dogs with CKD in uremic crisis subjected to IHD without bypass mode following the technique described by Cowgill [9], with body weights ranging from 16.2 to 48.5 kg. The IHD group with Bypass consisted of seven dogs with CKD in uremic crisis subjected to IHD in bypass mode adapted from Dufayet and Cowgill [6], with body weights ranging from 8 to 16.1 kg. Both groups were evaluated during the first session of IHD with and without bypass. Assessments were conducted pre-session, during the session, and post-session. Clinical evaluations were performed on the day following the session to detect clinical signs related to dialysis disequilibrium syndrome (nausea, vomiting, tremors, restlessness, nystagmus, seizures, or coma).

Clinical treatment

The clinical treatment was performed on all the animals from the first consultation and maintained according to the individual needs of each patient, even during the period of intermittent hemodialysis sessions. The therapeutic management was individualized and included intravenous fluid therapy, gastrointestinal support with control of vomiting and gastric acidity, treatment of anemia, supplementation of potassium and sodium bicarbonate, management of arterial hypertension, and control of hyperphosphatemia when necessary.

Intravenous fluid therapy was carried out with Ringer's Lactate solution for volume replacement, following the approach outlined by Davis et al. [20].

Emesis control was conducted with antiemetics such as ondansetron (0.5–1.0 mg/kg, IV, every 8–12 h) or maropitant citrate (1 mg/kg, SC, every 24 h) for more severe cases. For gastric acidity reduction, omeprazole (1 mg/kg, IV, every 24 h) was used.

Supplementation with recombinant human erythropoietin (100 IU/kg, SC, three times weekly) commenced when the hematocrit dropped below 20%, concurrent with injectable iron supplementation (100 mg per animal every 21 days). After reaching the target hematocrit (30%), the erythropoietin frequency was adjusted to twice weekly [21, 22].

Potassium replacement (potassium chloride 19.1%) was performed with Ringer's lactate fluid therapy in animals with concentrations less than 5.5 mEq/L at the post-session if necessary. In cases of lower bicarbonate levels at the post-session (pH < 7.2 and serum bicarbonate < 12 mmol/L), sodium bicarbonate replacement (sodium bicarbonate 8.4%) was administered IV to animals in the IHD without bypass group.

Hypertension control addressed systolic blood pressure (SBP) exceeding 160 mmHg [3], utilizing antihypertensives such as amlodipine (0.1 to 0.25 mg/kg every 12–24 h orally) and/or benazepril (0.25–0.5 mg/kg every 12–24 h orally).

Aluminum hydroxide therapy was initiated when plasma phosphorus concentrations remained elevated (above 4.6 mg/dL in CKD II, above 5 mg/dL in CKD III, and above 6 mg/dL in CKD IV), at a dosage of 30 to 90 mg/kg per day, divided across total meals in conjunction with a therapeutic kidney diet [23].

Intermittent Hemodialysis

Intermittent hemodialysis sessions were conducted at the Dialysis Center of the College of Veterinary Medicine and Animal Science, Unesp, Botucatu. All animals were catheterized with a 12 Fr, 20 cm double-lumen catheter (Joline GmbH & Co®) placed in the right external jugular vein, positioned in the cranial vena cava or the right atrium entrance, as outlined by Bloom and Lobato [8].

Lateral radiographic assessment of catheter placement was performed in all animals. The dogs were kept on a padded stainless-steel table during the dialytic process, with manual restraint when needed.

The activated clotting time (ACT) for each animal was determined via an ACT monitor following the manufacturer's guidelines. Initial anticoagulation involved sodium heparin at a dose of 50 IU/kg, and its reapplication was halted if clotting time exceeded 1.6 to 2 times the normal reference interval for the species [8].

For the IHD group without bypass, capillary hemodialysis filters with 0.8 m^2, 1 m^2, and 1.3 m^2 Polysulfone® Fresenius membranes were used, as recommended by Cowgill [9]. For the IHD group with bypass, capillary hemodialysis filters with a 0.8 m^2 Polysulfone® Fresenius membrane were utilized [9].

A hemodialysis machine model 4008 F with ultrafiltration control (Fresenius Medical Care®) was used, connected to a reverse osmosis water treatment unit.

All animals included in the study were within the range of 400–700 mg/dL of urea. The dialytic prescription was carried out in steps:

Step 1: Treatment intensity was defined by the total urea reduction ratio (URR total), per-hour URR (URR/h) and session time (hours). Based on the urea values of the animals in the study, the target URR for the first session was set to a maximum of 50%, in accordance with the recommendation by Cowgill [9]. The total volume of blood in liters to be dialyzed during the session, the blood volume to be dialyzed per hour (L/h), and the blood volume to be dialyzed per minute (ml/min) were determined on the basis of the patient's body weight [9].

Step 2: In animals in which Qb (mL/min) was less than 60 mL/minute, an average Qb of 63 mL/min was determined and considered the chosen Qb. All animals in which this modification was applied were assigned to the IHD group with bypass (Fig. 1**).**

Step 3: After dialysis prescription determination (steps 1 and 2), the "bypass" was determined. Each session hour was named a cycle (60 min) and divided into three moments (each lasting 20 min). Within each moment, the minutes of dialysis and minutes without exchange (bypass) were calculated, adding up to 20 min for each moment.

To determine the volume of blood passing through the dialyzer during each Bypass moment within each cycle, the number of moments (three) was multiplied by the constant "80" (mL) for Fresenius F4 filters (Fresenius Medical Care®) (0.8 m^2 surface area) adapted from Dufayet and Cowgil [6]. Subtracting this result from the total blood volume, the blood volume to be dialyzed in each cycle (mL/cycle) was obtained (Fig. 2**).**

The blood volume dialyzed in each cycle (ml/cycle) was divided by the number of moments (three) (ml/moment), and this result was divided by the chosen Qb, yielding the time (in minutes) in which the blood remained in dialysis within each moment. The bypass time was obtained by subtracting the dialysis time within each moment from the total moment time (20 min) (Fig. 3).

The dialysate consisted of 8.4% sodium bicarbonate buffer solution, 2 mEq/L of potassium, and CPHD 22G/34 electrolyte solution with glucose (Fresenius Medical Care®) to prevent hypoglycemia, along with ultrapure water. Sodium adjustments during intermittent renal replacement therapy sessions were in line with Cowgill [9] to minimize the risk of imbalance syndrome and/or hypotension. The dialysate flow was set at 500 mL/min for both groups [9].

Human arterial and venous lines for hemodialysis of 6 mm (pediatric) or 4 mm (neonatal) were used. The line size selected was a maximum limit of 10% of the total extracorporeal blood volume, considering the blood volume filling the hemodialyzer [11].

Session monitoring parameters

Throughout the entire dialysis session, the clinical parameters of all the animals in both groups were evaluated. Parameters such as heart rate, respiratory rate, rectal temperature (T°C), and SBP were assessed pre-session (M0), 30 min (M1), 60 min (M2), and 120 min after the session began (M3), and 10 min post-session (M6) (Fig. 4).

Qb data were also analyzed at 30 min (M1), 60 min (M2), and 120 min (M3). ACT data and the administered heparin dose were assessed pre-session (M0), 60 min (M2), 120 min (M3), 180 min (M4), and 240 min after the session began (M5) (Fig. 4).

Laboratory examinations

Samples were collected and analyzed at M0 and M6 in the IHD with and without bypass groups (Fig. 4). A total blood volume of 5 mL was collected via jugular venipuncture. Specifically, 0.5 mL was immediately stored in sterile tubes with 7.5% EDTA anticoagulant for complete blood count (CBC) determination. For serum separation, 3.5 mL of blood was collected in anticoagulant-free tubes and centrifuged at 2,059 RCF for 15 min to determine the serum concentrations of urea, creatinine, total protein, albumin, and phosphorus. An additional 1 mL was collected for venous blood gas analysis in a heparinized syringe.

The values for red blood cells, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelets, and total leukocytes were obtained via the hematological analyzer Poch-100iV Diff (Roche Diagnóstica Brasil Ltda). Total protein determination was performed manually via a refractometer. Leukocyte differentiation was conducted

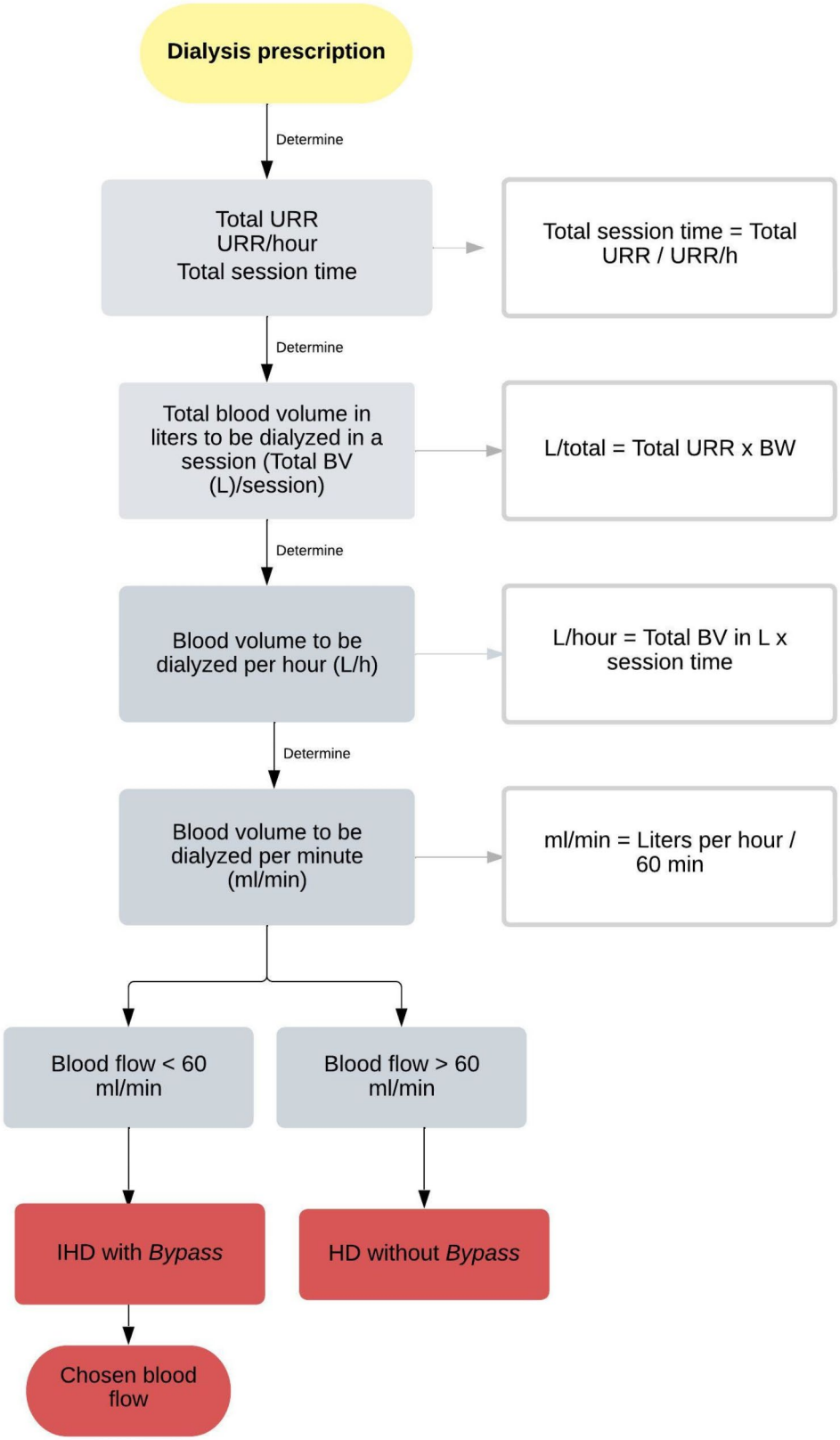

Fig. 1 Flowchart illustrating steps 1 and 2 of the dialytic prescription for animals undergoing intermittent hemodialysis with and without bypass

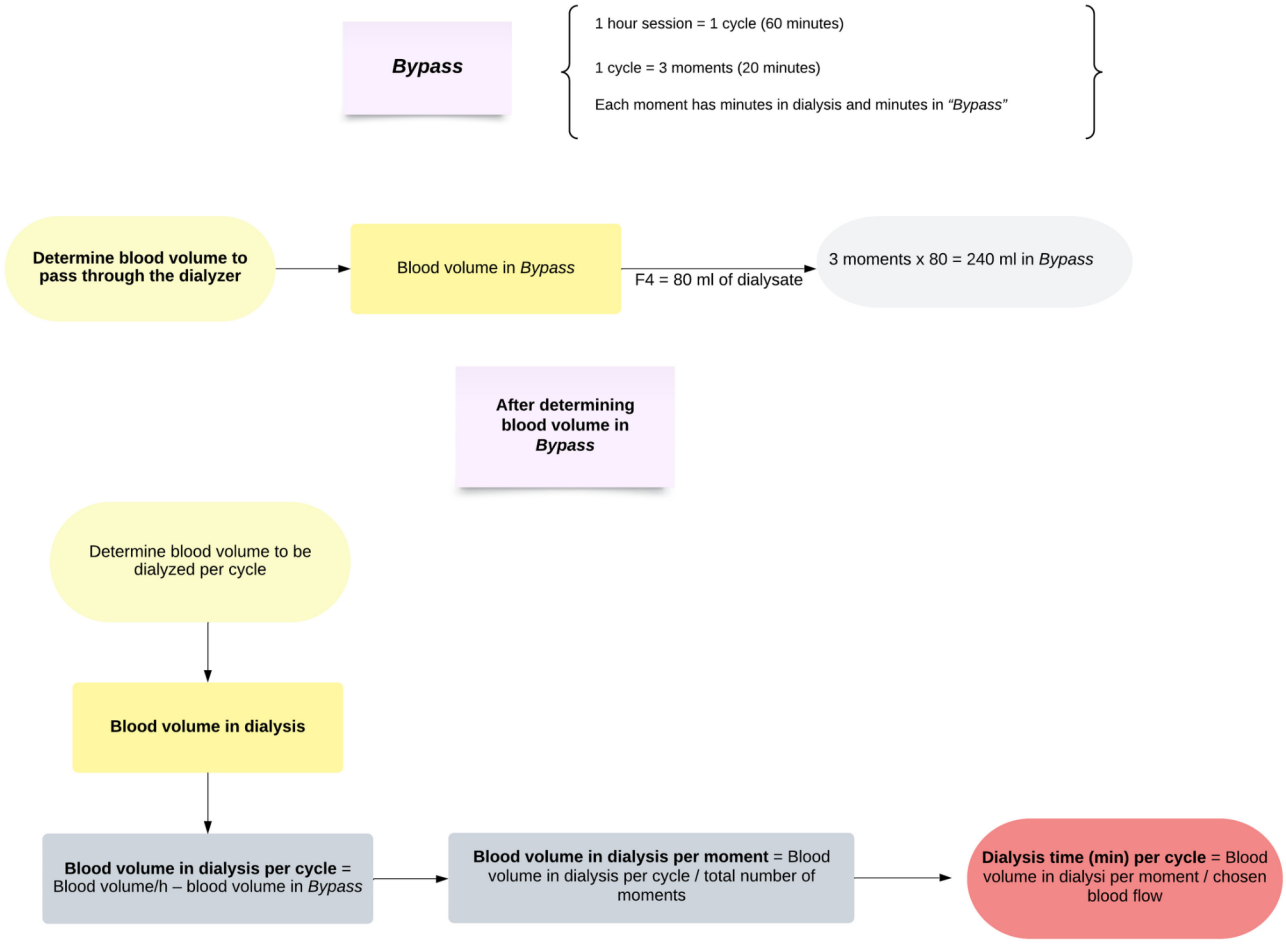

Fig. 2 Flowchart illustrating steps 3 and 4 of the dialytic prescription for animals undergoing intermittent hemodialysis without bypass

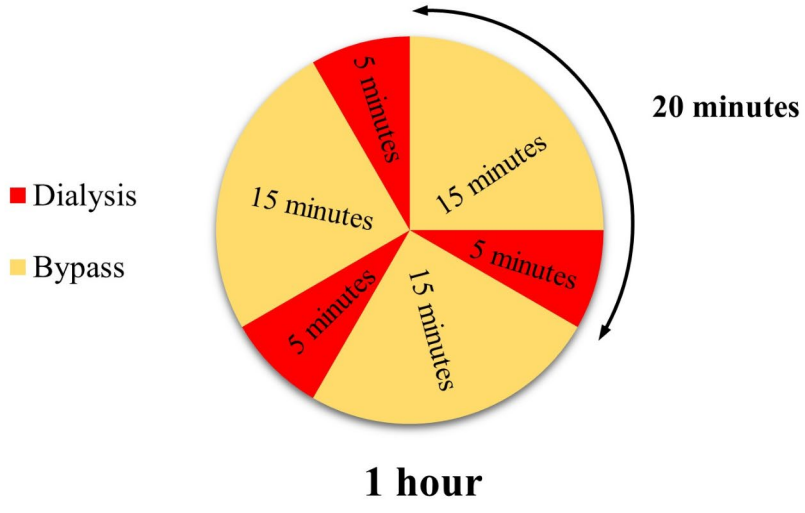

Fig. 3 Schematic representation of moments within an hour of an intermittent hemodialysis session with bypass
Notes: The illustration depicts an hour session using Fresenius F4®. The session includes moments of effective exchange (red) between the blood and dialysate and moments of bypass (yellow) where exchanges are interrupted. The duration of bypass and dialysis can be adjusted as desired, respecting the 20-minute intervals within each moment

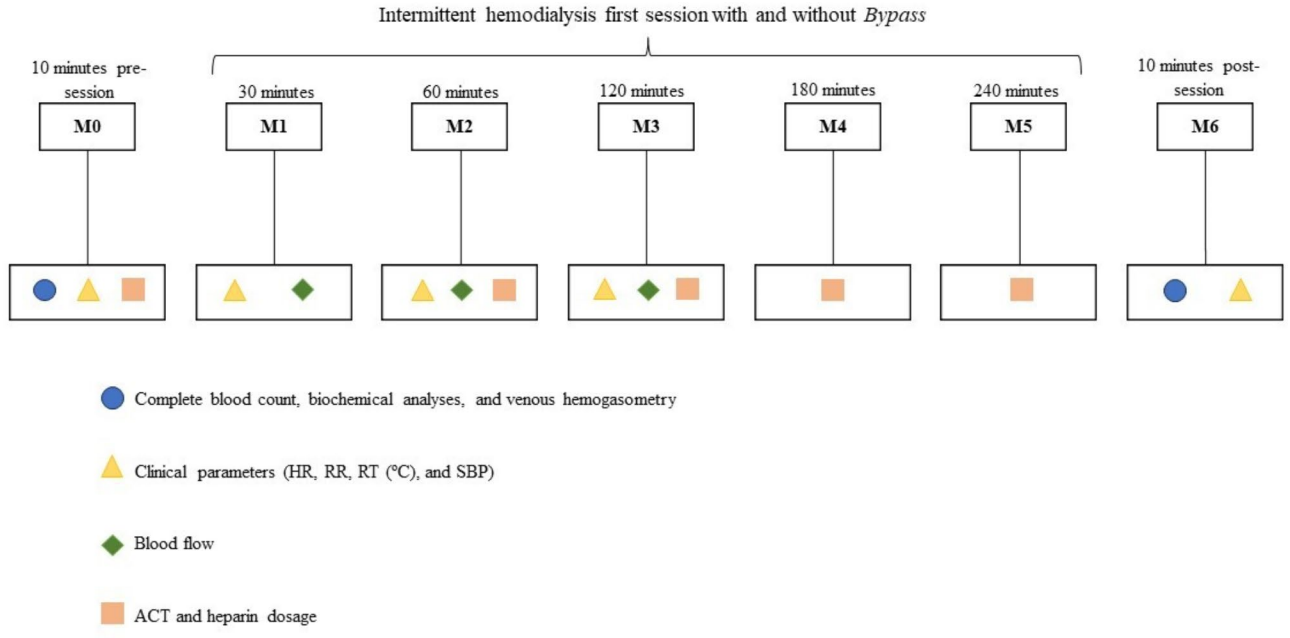

Fig. 4 Experimental timeline depicting the acquisition and evaluation of session data and blood samples from the IHD without bypass and IHD with bypass groups
Note: M0 (10 min pre-session); post-session beginning moments: M1 (30 min), M2 (60 min), M3 (120 min), M4 (180 min), M5 (240 min); and M6 (10 min post-session)

on Wright-stained blood smears, which were examined under an oil immersion objective (x100) via a microscope. Blood gas analysis was carried out via a benchtop blood gas analyzer (ABL9 blood gas analyzer, Biodina Rio Representações Ltda).

All serum biochemical determinations were conducted via automated equipment in accordance with the manufacturers' specifications for reagents and commercial kits.

Statistical analysis

The sample size was determined based on a statistical power analysis, aiming to ensure sufficient power to detect significant differences between the groups, considering the expected effect size, significance level, and variability parameters.

Assumptions of normality and homoscedasticity were evaluated via the Shapiro–Wilk and Levene tests, respectively. Comparisons between moments of each group (M0 × M6), as well as between moments within groups (M0 IHD group without bypass × M0 IHD group with bypass and M6 IHD group without bypass × M6 IHD group with Bypass), for variables related to CBC, blood gas analysis, and biochemistry were performed via parametric analysis (paired t test, unpaired t test) and nonparametric analysis (Wilcoxon and Mann–Whitney tests) as appropriate. The results are presented as the means ± standard errors of the means (SEM) and medians (Q1 and Q3) when parametric and nonparametric tests were used, respectively. Statistical significance was considered for $P < 0.05$.

Comparisons between the IHD with bypass group and the IHD without bypass group for variables such as body weight, session time, URR, and a modified approach to ACT in which time was not considered were conducted via unpaired t test and Mann–Whitney test, respectively. The results are presented as the mean ± SEM. Statistical significance was considered for $P < 0.05$.

Variables such as heart rate, respiratory rate, rectal temperature (°C), and SBP were analyzed via a mixed model for repeated measures over time. Group and time, along with their interaction, were considered fixed effects. The results are presented as the mean ± SEM, and $P < 0.05$ was considered statistically significant.

The differences in the Qb variables were compared via inference analysis with generalized linear mixed models (GLMMs from SAS) (Proc Glimmix). Covariance matrices were selected on the basis of criteria such as Akaike's information criterion (AIC), consistent Akaike's information criterion (AICC), and Bayesian information criterion (BIC). Group, time, and group × time were considered fixed effects. The PDIFF command was used to compare adjusted means with the Tukey post hoc test. The results are presented as the mean ± SEM, and $P < 0.05$ was considered statistically significant (https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.5/statug/statug_glimmix_syntax13.htm).

The variables ionized calcium (iCa), ACT, and heparin were analyzed via descriptive analysis.

Abbreviations

CKD	Chronic kidney disease
IHD	Intermittent hemodialysis
MCV	Mean corpuscular volume
MCHC	Mean corpuscular hemoglobin concentration
ACT	Activated clotting time
URR	Urea reduction ratio
DDS	Dialysis disequilibrium syndrome
SBP	Systolic blood pressure
CBC	Complete blood count
AIC	Akaike's information criterion
AICC	Consistent Akaike's information criterion
BIC	Bayesian information criterion
ICa	Ionized calcium

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12917-025-04735-7.

Supplementary Material 1

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Author contributions

MGPA and PTCG-O contributions to the conception and design of the study and the initial manuscript draft. MGPA, SRM, RSM, SSG, HDMG, RKT, ASO, RLAF and AM conducted material preparation, data collection, and analysis. All authors providing input on previous versions, reviewed and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee (Comitê de Ética no Uso de Animais - CEUA) of the Faculty of Veterinary Medicine and Animal Science, UNESP (protocol number 0084/2021). Prior to admitting the dogs, informed consent forms were obtained from all owners, permitting the use of all clinical data generated during their visit to the veterinary hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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