Received: 2 April 2021 | Accepted: 23 November 2021

DOI: 10.1111/jvim.16337

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Plasma sodium and potassium concentrations after hypophysectomy in dogs with corticotroph adenomas

Sara Del Magno[1] | Sarah van Rijn[2] | Stefano Azzariti[3] | Chiara Valtolina[2] | Jiske l' Ami[4] | Björn P. Meij[2]

[1]Department of Veterinary Medical Sciences, School of Agriculture and Veterinary Medicine, University of Bologna, Ozzano dell'Emilia, Italy

[2]Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

[3]Department of Clinical Sciences and Services, Royal Veterinary College, Hertfordshire, United Kingdom

[4]IVC Evidensia Nederland, Vleuten, The Netherlands

Correspondence
Björn P. Meij, Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 108, 3584 CM Utrecht, The Netherlands.
Email: b.p.meij@uu.nl

Abstract

Background: Electrolyte abnormalities, especially hypernatremia, are frequent complications after transsphenoidal hypophysectomy in dogs with pituitary-dependent hypercortisolism.

Objectives: To describe electrolyte abnormalities after transsphenoidal hypophysectomy and to investigate possible associations between postoperative hypernatremia and clinical and surgical variables as well as with postoperative outcome.

Animals: One hundred and twenty-seven client-owned dogs.

Methods: Dogs with pituitary corticotroph adenomas that underwent transsphenoidal hypophysectomy were retrospectively included. Plasma sodium and potassium concentrations were measured −2, +2, +8, +24, and +48 hours from hypophysectomy. Clinical (breed, age, body weight, skull type, urinary cortisol/creatinine ratio, percentage of suppression to dexamethasone) and surgical variables (duration of anesthesia and surgery, pituitary dimensions) were compared to the development of hypernatremia.

Results: Postoperative hypernatremia developed in 46.5% (57/127) of dogs and hyponatremia in 6.3% (8/127). Plasma sodium concentration increased after surgery and peaked at 8 hours after surgery, normalizing after 24 to 48 hours. Plasma potassium concentration increased without exceeding the reference limit.

No significant associations were found between clinical and surgical variables and hypernatremia, or between hypernatremia and postoperative death, long-term survival or recurrence.

Surgery time was significantly longer in dogs that developed persistent diabetes insipidus ($P = .02$) and persistent diabetes insipidus occurred more frequently in dogs with enlarged pituitary glands ($P = .01$).

Conclusion and Clinical Importance: Hypernatremia remains a frequent postoperative complication after transsphenoidal hypophysectomy but did not appear to have an impact on postoperative outcome. No predisposing factor to postoperative

Abbreviations: ACTH, adrenocorticotropin hormone; AVP, arginine vasopressin; CT, computed tomography; DI, diabetes insipidus; MRI, magnetic resonance imaging; P/B value, pituitary height-to-brain area value; PDH, pituitary-dependent hypercortisolism; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; UCCR, urinary cortisol/creatinine ratio

hypernatremia was identified. Variations in plasma potassium concentrations do not seem to influence postoperative outcome.

KEYWORDS
Cushing's disease, diabetes insipidus, electrolyte, hypernatremia, pituitary adenoma

1 | INTRODUCTION

The most common pituitary neoplasm in dogs is the adrenocorticotropin hormone (ACTH)-secreting adenoma, or corticotroph adenoma, that usually causes pituitary-dependent hypercortisolism (PDH, Cushing's disease). In humans, Cushing's disease usually is caused by a microadenoma and selective surgical removal of the adenoma is considered the treatment of choice, leaving unaffected pituitary tissue in situ.[1] In dogs, microadenomas usually are treated medically, whereas enlarged pituitary glands more frequently are treated by surgery, radiation therapy, or both.[2-4] The aim of pituitary surgery in dogs is generally complete hypophysectomy because it is difficult to recognize unaffected pituitary tissue during surgery.[5,6] Transsphenoidal hypophysectomy has been reported as an effective treatment for pituitary neoplasia in dogs.[2,7-9]

After hypophysectomy, hormone substitution treatment is started. Dogs need lifelong hormone replacement with cortisone acetate and thyroxine and temporary administration of desmopressin, a vasopressin analogue to treat diabetes insipidus. In a population of healthy experimental dogs undergoing transsphenoidal hypophysectomy, discontinuation of desmopressin 1 week postoperatively was well tolerated.[10] In a clinical context, however, diabetes insipidus may persist after hypophysectomy and supplementation with desmopressin is needed for a prolonged period (53% of cases) or life-long (22%).[2,7] This finding is related to pituitary gland size, and persistent diabetes insipidus was observed more frequently in hypophysectomized dogs with enlarged pituitary glands than in those with normal-sized pituitary glands.[2,7]

Considering all of the hormonal changes after hypophysectomy, it is therefore not surprising that both in dogs and humans postoperative complications related to electrolyte imbalances frequently are reported.[7,11] In dogs, the most frequent postoperative complication is hypernatremia.[7] Since the development and clinical introduction of the surgical technique for transsphenoidal hypophysectomy in dogs with PDH,[10] a pre- and postoperative protocol for IV fluid administration was applied and included monitoring of serum electrolyte concentrations, especially sodium and potassium, at defined time points.[7] Electrolyte derangements in the postoperative period represent a challenge for the management of these patients, especially in the event of severe hypernatremia. These difficulties may represent a possible limitation to the popularity of the surgical technique and a better understanding of electrolyte imbalances in the postoperative period could help in the management of these patients. The reason why some dogs develop severe hypernatremia and others do not remains unknown. In previous studies, plasma potassium concentration usually tended to increase in concentration in the postoperative period without exceeding reference limits.[7] No investigations have been performed about a possible influence of plasma potassium concentrations in relation to surgical variables and outcome.

An improvement in postoperative outcome over time has been reported previously for patients that had transsphenoidal hypophysectomy, possibly because of increased experience of surgeons and clinicians.[8,12]

Our aim was to describe electrolyte (sodium and potassium) imbalances in the perioperative period of transsphenoidal hypophysectomy in dogs with corticotroph adenomas and to detect correlations between electrolyte imbalances and clinical and surgical variables. The second aim was to investigate if postoperative electrolyte imbalances are correlated to worse outcome in terms of postoperative death, survival time or recurrence rate.

2 | MATERIALS AND METHODS

One-hundred and twenty-seven dogs presented to the Utrecht University Small Animal Clinic with a diagnosis of pituitary-dependent hypercortisolism or corticotroph adenoma that underwent transsphenoidal hypophysectomy between July 2005 and June 2015 were included in the study. Dogs with complete medical records were included and the data were retrospectively reviewed.

Given the long period of inclusion and the experience acquired over the years in the perioperative management of these patients, that possibly could have influenced the electrolyte imbalances and outcome, dogs were divided into 2 groups, based on date of surgery in the first 5 years (2005-2010) or last 5 years (2011-2015) of the study period. The 2 time period cohort groups were compared in clinical and outcome variables.

The dogs included were classified according to skull morphology as dolichocephalic, mesaticephalic and brachycephalic.[13] Mixed breed dogs were classified by the surgeon (BPM) according to their skull morphology.

In all patients, CBC and biochemical profiles were performed. Hypercortisolism was diagnosed based on clinical signs and increased urinary cortisol-creatinine ratios (UCCRs; reference range, $<8.3 \times 10^{-6}$) in 2 consecutive urine morning samples collected at home. After collection of the second sample, 3 PO doses of dexamethasone (0.1 mg/kg) were administered at 8 hours-interval and the next morning a third sample of urine was collected. If the UCCR of the third sample was <50% of the mean value of the first 2 samples, a diagnosis of PDH was confirmed.[14] In dogs where no suppression occurred, the pituitary origin of the hypercortisolism was supported by measurement of normal or increased plasma ACTH concentrations. In dogs in which UCCR was

not measured, diagnosis was based on the low dose dexamethasone suppression test and pituitary imaging.[15]

Advanced diagnostic imaging of the skull was performed in all cases by computed tomography (CT) or magnetic resonance imaging (MRI) to confirm the presence of a pituitary adenoma, to measure the pituitary height, width and length, to calculate the pituitary height-to-brain area value (P/B value) and to visualize surgical landmarks.[16] Dogs with a P/B value >0.31 were considered to have an enlarged pituitary gland, whereas in dogs with a P/B value ≤0.31 the pituitary gland was considered normal-sized.[16]

Transsphenoidal hypophysectomy was performed in all dogs by the same surgeon (BPM) according to the microsurgical technique described previously.[10] During surgery, the administered IV fluids consisted of Sterofundin ISO (BBraun Vet Care GmbH, Tuttlingen, Germany; 5-10 mL/kg IV). The duration of anesthesia and surgery was recorded.

Plasma sodium and potassium concentrations were measured before (−2 hours) and after (+2, +8, +24, +48 hours) removal of the pituitary gland. More frequent evaluation of electrolytes, in case of abnormal plasma sodium concentrations, was left to the discretion of the intensive care specialist in charge. Blood samples were collected from a central venous catheter placed just before surgery. Sodium and potassium were measured in plasma using an ion selective electrode (Backman Coulter AU 680). Normal reference ranges for sodium were 141-150 mmol/L and for potassium were 3.6-5.6 mmol/L. Hypernatremia was defined when plasma sodium concentration exceeded 150 mmol/L, and hyponatremia when plasma sodium concentration was lower than 141 mmol/L. Dogs that were hypernatremic before surgery (−2 hours) were excluded from further analysis of plasma sodium concentrations.

Postoperative fluid therapy consisted of administration of a maintenance low sodium fluid (Sterofundin BG; B.Braun Vet Care GmbH, Tuttlingen, Germany) and of an isotonic balanced fluid (Sterofundin ISO; B.Braun Vet Care GmbH, Tuttlingen, Germany) to correct ongoing losses in the urine in case of polyuria (compositions of the 2 types of fluids are given in Appendices A and B). The fluid rate was adjusted to urine output, which was monitored using a Foley catheter connected to a closed urinary collection system, and to fluid balance. In the event of increased plasma sodium concentration (150-165 mmol/L), a hypotonic solution containing low sodium (0.45% NaCl +2.5% glucose) or no sodium (glucose 5%) was added to replenish the free water deficit and correct the hypernatremia. One drop of desmopressin 0.01% (Minrin, nasal drops, Ferring B.V., Hoofddorp, the Netherlands) was administered in the conjunctival sac of 1 eye at the end of surgery and continued q8h in the postoperative period (2 weeks). In case of progressive hypernatremia and polyuria that was difficult to correct solely by adjustment of fluid therapy or in case of severe hypernatremia (>165 mmol/L), an additional drop of desmopressin was administered in the conjunctival sac and then administered every 6 hours, together with fluid correction to gradually reach normal plasma sodium concentration. Hydrocortisone (Solu-cortef, Upjohn, Ede, the Netherlands) was administered IV at 1 mg/kg q6h until the dog was able to eat and drink, and then replaced by PO cortisone acetate (Cortisoni Acetas, Genfarma, Maarssen, the Netherlands; 1 mg/kg PO q12h, tapered gradually to 0.25 mg/kg PO q12h). Thyroxine (Forthyron, Eurovet Animal Health BV, Bladel, the Netherlands) was supplemented as soon as the dog could eat at a starting dose of 15 μg/kg q12h. After 2 weeks, desmopressin was discontinued and the owner asked to monitor the amount of water consumed. In case of polydipsia and polyuria, desmopressin administration was resumed and diabetes insipidus was considered persistent.

The UCCRs were measured in morning urine samples at 2, 8 weeks, 6 months and once a year after surgery, each time 24 hours after the dog had received cortisone acetate. In the event of clinical signs indicative of hypercortisolism, UCCRs were determined more frequently. Residual disease was defined when UCCR was $\geq 10 \times 10^{-6}$ within 2 months after surgery or in case of incomplete hypophysectomy confirmed on imaging within 2 months after surgery. Remission was defined as UCCR $< 10 \times 10^{-6}$ within 2 months after surgery together with resolution of clinical signs of hypercortisolism. Recurrence was defined as UCCR $\geq 10 \times 10^{-6}$ after initial remission was achieved.[12]

All postoperative deaths within 4 weeks after surgery were defined as surgically-related death regardless of the cause of death.

Long-term follow-up was obtained by periodic reevaluations or by telephone interviews with the owner or referring veterinarian. In particular, recurrence of clinical signs, persistence of diabetes insipidus, survival and cause of death were recorded.

All statistical analyses were made using IBM SPSS Statistic for Windows, Version 24.0. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests and plotting of histograms, and in the event data were not normally distributed, nonparametric tests were used accordingly. Changes in plasma sodium and potassium concentrations over time were evaluated using the Wilcoxon Signed Ranks Test. Differences in clinical variables, electrolyte concentrations and development of diabetes insipidus between dogs with enlarged and normal-sized pituitary glands and between dogs that died or survived beyond 4 weeks after surgery were calculated using Mann-Whitney U tests. This test also was used to compare development of persistent diabetes insipidus in dogs with or without hypernatremia. Correlations between quantitative data were calculated using Spearman's rho tests. For comparison of sodium concentrations between dogs with different skull types, a 1-way analysis of variance (ANOVA) was used. Survival interval was calculated as the time between the date of surgery and death. Disease-free interval was calculated as the interval between the date of surgery and the diagnosis of recurrence or the last date on which hypercortisolism was known to be in remission. Dogs that died from unrelated causes from 4 weeks postsurgery onward or that were still alive at the time of follow-up were censored. Survival analysis was performed using Kaplan-Meier curves and the log rank test was used to assess significance. Significance was set at $P < .05$.

3 | RESULTS

3.1 | Demographic data

One-hundred and twenty-seven dogs (66 male, 29 castrated; 61 female, 52 spayed) with a diagnosis of PDH or corticotroph adenoma that

underwent transsphenoidal hypophysectomy were included in the study. Median age at the time of surgery was 8.7 years (range, 2.7-14 years); median body weight was 19.7 kg (range, 3.7-63 kg). The most common breeds were Beagle (9 dogs), Labrador Retriever (7 dogs), Dachshund (7 dogs) and Maltese (7 dogs), and 23 dogs were mixed breeds.

There were 85 mesaticephalic, 27 brachycephalic and 9 dolichocephalic dogs. For 6 mixed breed dogs no information about skull shape was available. Median height of the pituitary gland was 7.6 mm (range, 2-22.5 mm), median length was 8.4 mm (range, 2.2-21.6 mm) and median width 8.6 mm (range, 3.8-25.6 mm). Imaging identified an enlarged pituitary gland (P/B value >0.31) in 106 dogs (83%) with a median P/B value of 0.5 (range, 0.32-1.4), and a normal-sized pituitary gland (P/B ≤ 0.31) in 21 dogs (17%) with a median P/B value of 0.28 (range, 0.13-0.31).

Eighty-six dogs underwent surgery in the period 2005-2010 and 41 in the period 2011-2015. No significant difference was found between the groups for age, body weight, sex, skull type and P/B ratio.

3.2 | Diagnostic evaluation

Median preoperative UCCR was 115.6×10^{-6} (range, $1.7\text{-}763 \times 10^{-6}$; reference range, $<8.3 \times 10^{-6}$), median UCCR after suppression with dexamethasone was 47.6×10^{-6} (range, $0.2\text{-}711 \times 10^{-6}$) and median percentage of suppression was 62% (range, −162.1-99.3%). The dog with preoperative UCCR of 1.7 was later diagnosed with a non-functional corticotroph adenoma. For 13 dogs, UCCR values were not available and diagnosis of PDH was based on the low dose dexamethasone suppression test and pituitary and adrenal imaging.

A CT scan of the skull was available for surgical planning for 125 dogs, whereas in 2 dogs MRI was performed.

3.3 | Surgery and postoperative period

Median duration of surgery in 110 patients was 147 minutes (range, 75-381 minutes). For 17 dogs, the duration of surgery was not recorded. Median duration of anesthesia in 115 dogs was 256 minutes (range, 155-460 minutes). For 12 dogs, the duration of anesthesia was not recorded.

Plasma sodium concentration was higher than the reference range (141-150 mmol/L) in 6 dogs at 2 hours before surgery. These dogs were excluded from further analysis of plasma sodium concentration. In the remaining 121 dogs, median plasma sodium concentration was 145 mmol/L preoperatively (range, 135-150 mmol/L). Plasma sodium concentration after hypophysectomy initially decreased at 2 hours postoperatively (median, 144 mmol/L; range, 129-160 mmol/L) and then increased to peak at 8 hours postoperatively (median 150 mmol/L; range, 133-180 mmol/L; Figure 1). Plasma sodium concentration at 2, 8, and 24 hours postoperatively was significantly different compared to preoperative plasma sodium concentration ($P = .002$, $P < .001$, $P = .001$, respectively) and was normal at 48 hours after surgery in 86/116 dogs (median, 146 mmol/L; range, 125-164 mmol/L), 16/116 dogs were hyponatremic and 14/116 dogs were hypernatremic. Hypernatremia (>150 mmol/L) developed in the study time period in 57/121 dogs (47.1%) whereas in 8/127 dogs (6.3%) hyponatremia (<141 mmol/L) was observed 8 hours after surgery. In 6/121 dogs, hypernatremia developed at +2 h, in 47/121 dogs at +8 h, and in 4/121 dogs at +24 hours. In 24 dogs, hypernatremia was present 24 h after surgery and in 14 dogs plasma sodium concentration still was increased at 48 hours (Table 1). The frequency of postoperative hypernatremia was not significantly different between the 2 time period cohorts ($P = .78$).

Plasma potassium concentration increased progressively in the postoperative period, without exceeding the reference range (3.6-5.6 mmol/L; Figure 2). Mean plasma sodium and potassium concentrations were not significantly different between dogs with enlarged pituitary glands and dogs with normal-sized pituitary glands at any time point (Figure 3; Table 1).

No significant correlations between plasma sodium concentrations at any time point and surgical variables (body weight, P/B ratio, UCCR, duration of surgery and anesthesia) were found (Figure 4). Plasma sodium concentrations at any time point were not significantly different among dogs with different skull types.

Body weight correlated positively with the duration of surgery (rho = 0.37, $P < .001$) and duration of anesthesia (rho = 0.32, $P < .001$). Surgery time and anesthesia time were significantly shorter in dogs that underwent surgery in the second time period group (2011-2015; $P < .001$).

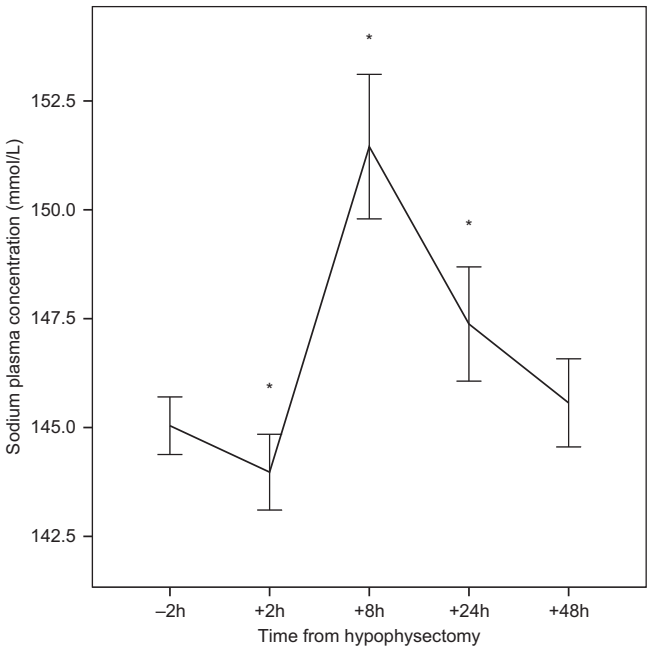

FIGURE 1 Median plasma sodium concentration (in mmol/L) at 2 hours preoperatively, and 2, 8, 24 and 48 hours postoperatively. Values at 2, 8 and 24 hours (*) were significantly different from preoperative values (−2 hours) ($P = <.001$) and normalized at 48 hours. Error bars represent the 95% confidence interval

TABLE 1 Median plasma sodium and potassium concentrations at −2, 2, 8, 24, 48 hr after hypophysectomy in 121 dogs with pituitary corticotroph adenomas (100 with enlarged and 21 with nonenlarged pituitary glands, 6 dogs with hypernatremia at −2 hr before surgery were excluded)

	Median plasma concentration (mmol/L)					
	Sodium			Potassium		
Time (hr)	Total (n = 121)	Enlarged (n = 100)	Nonenlarged (n = 21)	Total (n = 121)	Enlarged (n = 100)	Nonenlarged (n = 21)
−2	145 (135-150)	145 (135-150)	144.9 (141-149)	3.8 (2.0-5.1)	3.8 (2.0-5.1)	3.7 (2.8-4.7)
2	144 (129-160)	144 (129-154)	145 (137-160)	3.9 (2.5-5.8)	3.9 (2.5-5.8)	3.6 (2.8-4.8)
8	150 (133-180)	149 (133-180)	151 (141-157)	4.1 (3.2-5.6)	4.0 (3.2-5.6)	4.2 (3.1-5.1)
24	147 (136-179)	147 (136-179)	148 (139-175)	4.1 (3.1-5.0)	4.2 (3.1-5.0)	4.3 (3.4-4.8)
48	146 (125-165)	147 (141-164)	146 (125-165)	4.3 (3.0-7.0)	4.2 (3.0-7.0)	4.2 (3.6-5.8)

Note: Plasma sodium reference range 141-150 mmol/L and plasma potassium reference range 3.6-5.6 mmol/L.

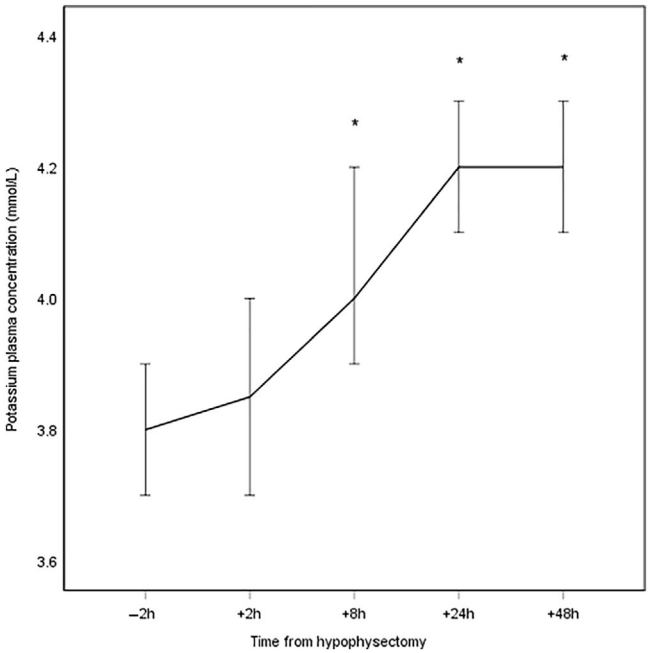

FIGURE 2 Median plasma potassium concentration (in mmol/L) at 2 hours preoperatively, and 2, 8, 24, 48 hours postoperatively. Values at 8, 24 and 48 hours after surgery were statistically different from preoperative values (*) ($P < .001$). Error bars represent the 95% confidence interval

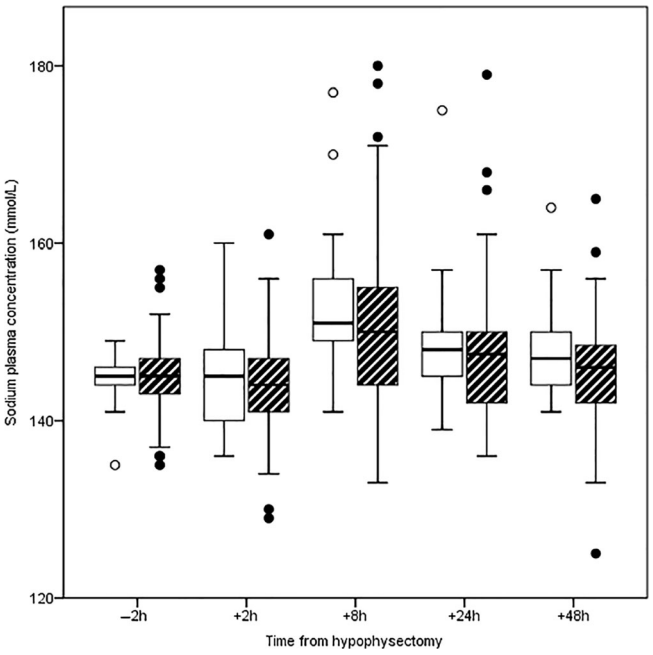

FIGURE 3 Boxplots displaying the plasma sodium concentrations (in mmol/L) 2 hours preoperatively, and 2, 8, 24, 48 hours postoperatively in dogs with enlarged and nonenlarged pituitary glands. No significant differences were present between dogs with enlarged and nonenlarged pituitary glands at any time point. Open boxes represent the nonenlarged pituitary gland group and striped boxes represent the enlarged pituitary gland group. The box represents the interquartile range (ie, from the 1st to 3rd quartile), the horizontal line represents the median value, the whiskers represent the lowest and highest value within 1.5× the interquartile range, • indicates an outlier for dogs with an enlarged pituitary gland and ° indicates an outlier for dogs with a nonenlarged pituitary gland

3.4 | Outcome

Overall postoperative survival rate was 89.8% (114/127 dogs). Of the 13 of 127 (10.2%) dogs that died within 4 weeks after surgery, 12 dogs had an enlarged pituitary gland (median P/B value 0.73; range, 0.39-1.4) and 1 dog had a normal-sized pituitary gland (P/B value, 0.29). No significant difference was found in postoperative plasma sodium concentration at 2, 8 or 24 hours after surgery ($P = .69$; .78; .6, respectively) between dogs that died within 4 weeks after surgery and dogs that survived after the 4-week time point. Nine dogs with enlarged pituitary glands died or were euthanized in the postoperative period, including 5 dogs for neurological problems (coma and stupor after surgery) and 4 dogs for dyspnea evaluated by thoracic radiographs (1 dog with aspiration pneumonia, 2 dogs with interstitial pneumonia, and 1 dog with pulmonary thromboembolism). Three dogs died after discharge from the hospital: 2 dogs with enlarged pituitary glands were euthanized because of general malaise, vomiting and acute abdominal pain and 1 dog because of

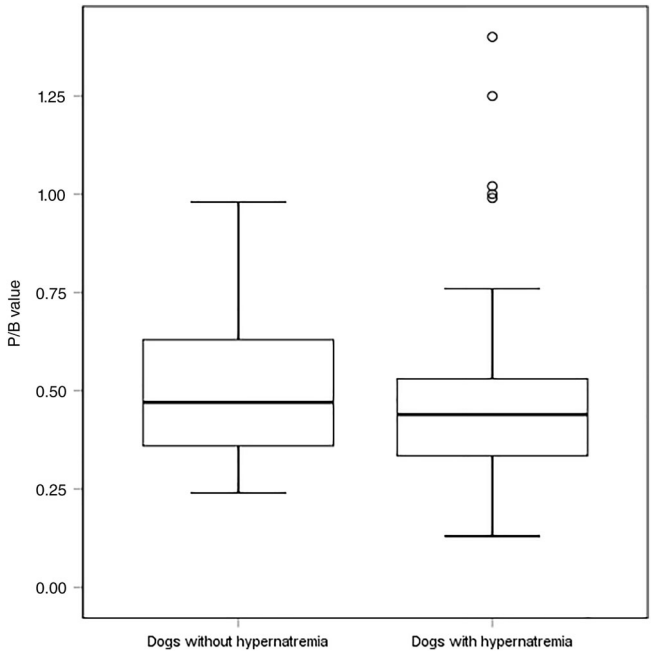

FIGURE 4 Boxplots displaying the pituitary height/brain area (P/B) values of dogs without postoperative hypernatremia and dogs with postoperative hypernatremia. The P/B value is not significantly different in dogs with or without postoperative hypernatremia ($P = .25$). The box represents the interquartile range (ie, from the 1st to 3rd quartile), the horizontal line represents the median value, the whiskers represent the lower and highest value within 1.5× the interquartile range, ° indicates an outlier for dogs with hypernatremia

suspected pulmonary thromboembolism and dyspnea 2 weeks after surgery. The dog with normal-sized pituitary gland died within 12 hours postoperatively because of dyspnea thought to be caused by pulmonary thromboembolism.

Survival time and disease-free interval were not significantly different between dogs with and without hypernatremia ($P = .6$ and $P = .5$; Figure 5A,B) and between the 2 time groups ($P = .64$ and $P = .27$, respectively). Median disease-free interval for this cohort (dogs in remission) was 354 days (range, 22-2558 days); median survival time was 370 days (range, 22-2558 days).

In the 114 dogs that survived beyond 4 weeks, persistent diabetes insipidus occurred in 81/114 (71.1%). In 68/81 dogs, the pituitary gland was enlarged and in 13 dogs the pituitary gland was normal-sized. The P/B value was significantly higher in dogs with persistent diabetes insipidus compared to dogs without persistent diabetes insipidus ($P = .01$; Figure 6).

No significant difference was found in plasma sodium concentration at any postoperative time point in dogs with persistent diabetes insipidus compared to dogs without persistent diabetes insipidus.

Surgery time was significantly longer in dogs that developed persistent diabetes insipidus ($P = .02$). No significant difference however was found in survival time and disease-free interval in dogs with and without persistent diabetes insipidus.

Residual disease occurred in 3 dogs in the postoperative period and was marked by persistent hypercortisolism. In 2 dogs, hypophysectomy was incomplete, whereas in the first dog the residual disease was diagnosed based on the UCCR at 2 and 8 weeks after surgery

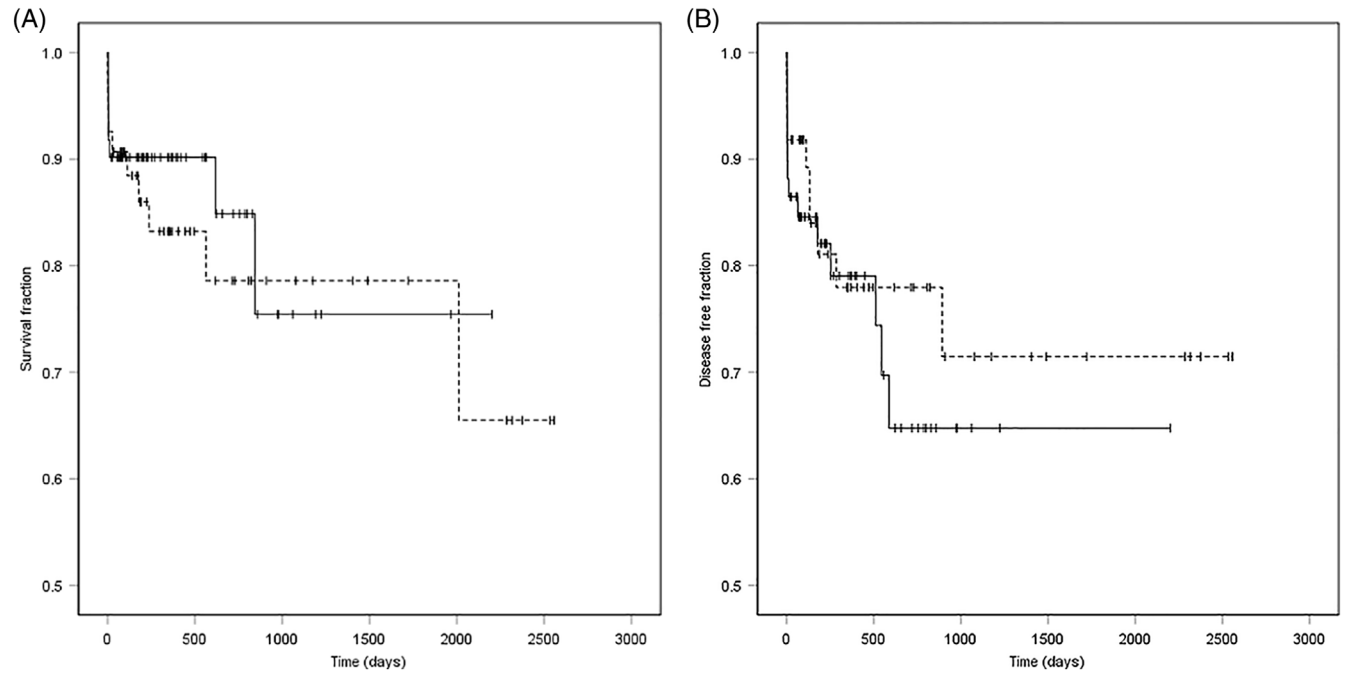

FIGURE 5 Kaplan-Meier survival curves. Survival time (A) and disease free interval (B) in days, comparing dogs without postoperative hypernatremia (continuous line) and dogs with postoperative hypernatremia (dotted line). Vertical bars indicate censored cases

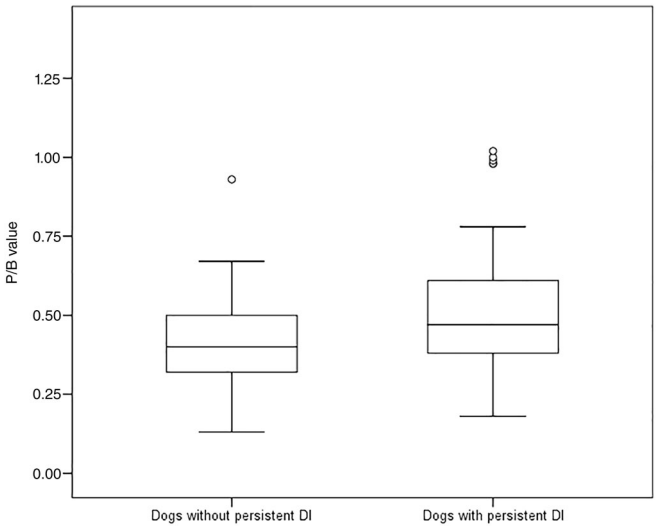

FIGURE 6 Boxplots displaying the pituitary height/brain area (P/B) values of dogs with and without persistent diabetes insipidus. The P/B value is significantly higher in dogs with persistent diabetes insipidus than in dogs without persistent diabetes insipidus ($P = .01$). The box represents the interquartile range (ie, from the 1st to 3rd quartile), the horizontal line represents the median value, the whiskers represent the lowest and highest value within 1.5× the interquartile range. ° indicates an outlier

(UCCR >10 × 10^{-6}). The P/B values in these 3 dogs were 0.24, 0.53, 0.76, respectively.

Postoperative remission was achieved in 112/114 dogs (98.2%) and recurrence occurred in 13/114 (11.4%) of the dogs during the follow-up period.

No significant association was found between postoperative plasma sodium and potassium concentrations and recurrences.

4 | DISCUSSION

We investigated changes in postoperative plasma sodium and potassium concentrations in dogs after hypophysectomy as a treatment for corticotroph adenomas. Hypernatremia frequently was observed in the postoperative period (46.5% of the dogs) with peak plasma sodium concentration 8 hours after surgery. Plasma potassium concentration gradually increased during the first 2 days after surgery without exceeding the reference range. Electrolyte imbalances after hypophysectomy were reported previously,[7] but their relationship with clinical variables and outcome was not investigated. Surprisingly, no correlations were found between hypernatremia on the one hand and clinical and surgical variables on the other hand, and thus no predisposing factors for the development of postoperative electrolyte imbalances were identified in our study. In addition, no association between hypernatremia and postoperative outcome was observed.

Increased plasma sodium concentrations after transsphenoidal hypophysectomy in dogs have been reported previously[7] and the factors that contribute to this finding include (a) marked polyuria and consequent free water loss associated with central diabetes insipidus, (b) initial resistance to exogenous administration of desmopressin at the receptor level in the distal tubules of the kidneys because of the increased plasma cortisol concentration in dogs with hypercortisolism at the time of surgery, and (c) concomitant administration of corticosteroids in the postoperative period. Central diabetes insipidus is a consequence of the lack of vasopressin because of the removal of the entire pituitary gland, including the neurohypophysis which is the storage site of vasopressin produced by the hypothalamus.[2,7] It is likely that in some dogs with large pituitary adenomas, preexisting central diabetes insipidus is unrecognized before hypophysectomy because of the dominant glucocorticoid-driven polyuria and polydipsia. After hypophysectomy, central diabetes insipidus is usually present for a period of 2 to 3 weeks during which time it is presumed that a neurovascular network is formed at the site where the pituitary gland was attached, gradually enabling vasopressin, produced by the hypothalamus, to be released again into the circulation.[7]

The median plasma sodium concentration at 2 hours after surgery was lower than the preoperative concentration. This finding was probably associated with intraoperative fluid administration and residual circulating endogenous vasopressin after removal of the pituitary gland. Endogenous vasopressin has a short half-life and is rapidly cleared from the circulation.

The results of our study must be interpreted with caution because the perioperative fluid therapy protocol has been adapted over time to optimize the prevention of electrolyte disturbances.[2,7] In the past, low-sodium fluid therapy (Sterofundin BG) was administered at a maintenance rate (50 mL/kg/day) in the postoperative period and dogs were stimulated to resume early PO fluid intake to compensate for fluid losses caused by postoperative polyuria associated with diabetes insipidus. This fluid protocol probably did not cover all fluid losses because not every dog started to drink or drank enough, leading to frequent hypernatremia in the postoperative period.[7] Eventually, the use of low-sodium fluids (Sterofundin BG) as maintenance together with isotonic electrolyte balanced fluids (Sterofundin ISO Vet Care GmbH, Tuttlingen, Germany) administered as 5% of body weight after surgery, and frequent postoperative monitoring (even every hour in cases with polyuria) of fluid balance to match ingoing fluids with urinary output and fluid losses, has decreased the frequency of hypernatremia in the postoperative period. Prompt correction of fluid imbalance in dogs that developed hypernatremia secondary to polyuria to replenish free water losses might be the reason for the lower frequency of hypernatremia in our study in comparison to previous studies.[7] The protocol used for the postoperative period to prevent or counteract hypernatremia appears to be effective, because the number of dogs that developed postoperative hypernatremia in our study was less than reported in a previous study, in which almost all dogs developed a mild hypernatremia.[7] Moreover, the hypernatremia in our study was of shorter duration than previously reported. Median plasma sodium concentrations after 24 and 48 hours were within the reference range (147.4 and 143.8 mmol/L, respectively), whereas in the previous study,[7] 24 hours after surgery median plasma sodium concentration was still increased (151.6 mmol/L).

No statistical difference was observed between survival of dogs that developed hypernatremia and dogs that did not. Additional studies are needed to explore how postoperative hypernatremia can be prevented because hypernatremia remains a challenging postoperative complication that can easily escalate out of control. With the support of an experienced intensive care unit, hypernatremia can be managed and resolved within 24 to 48 hours in most instances.

At 8 hours after surgery, 8.6% of dogs developed hyponatremia, although the same postoperative protocol was used as in the dogs in which hypernatremia was seen. Hyponatremia is a common complication after pituitary surgery in humans and is probably the consequence of syndrome of inappropriate secretion of antidiuretic hormone (SIADH), caused by damage or irritation of the neurohypophyseal or hypothalamic tracts, that occurs during selective removal of the tumor, leaving the unaffected pituitary tissue in place, or a consequence of underestimation of perioperative blood loss. In humans, a so-called 3 phase response has been described after sellar surgeries and includes an initial period of diabetes insipidus, followed by SIADH, followed by another period of diabetes insipidus.[17-19] In dogs, these syndromes are rarely observed because selective adenomectomy usually is not performed and the aim of surgery is complete hypophysectomy, including the neurohypophysis.[6]

In the first period after transsphenoidal hypophysectomy in dogs, the hypothalamic nuclei (supraoptic and paraventricular nuclei) that produce arginine vasopressin (AVP) are unable to release the hormone into the circulation. Surgical resection of the pituitary stalk and neurohypophysis, which represent AVP's physiologic pathway to the bloodstream, disconnects it from the circulation. As a result, the development of diabetes insipidus may cause large volume fluid losses, dehydration and hypernatremia. Diabetes insipidus typically lasted approximately 2 weeks in healthy experimental dogs that underwent hypophysectomy,[10] whereas in most of the dogs with pituitary-dependent hypercortisolism it took 15 days to months for AVP to again reach the circulation.[7] In most of the dogs, diabetes insipidus is transient if the axonal resection, performed during removal of the pituitary gland, is not too close to the hypothalamic nuclei and no ascending degeneration occurs.[7] Hypothalamic damage and nuclear degeneration could lead to irreversible inability of AVP to find a new way to reach the systemic circulation, resulting in permanent diabetes insipidus. However, other compensatory mechanisms might play important roles in resuming the activity of AVP, and some of these have not yet been fully investigated.[20]

Persistent diabetes insipidus was observed in 71.1% (81) of the dogs in our study, which compares favorably with 58% of prolonged diabetes insipidus and 23% of life-long diabetes insipidus reported previously.[2] In our study, the group with persistent diabetes insipidus included all the dogs that required administration of desmopressin for >2 weeks and no distinction was made between prolonged or life-long diabetes insipidus, because of the retrospective nature of the study. Sixty-eight of the 81 dogs that experienced persistent diabetes insipidus had enlarged pituitary glands, whereas 13 dogs had normal-sized pituitary glands. Persistent diabetes insipidus already has been reported in dogs surgically treated for large pituitary tumors, because dorsal extension of the tumor may cause chronic compression of the hypothalamic nuclei.[2] Damage to the hypothalamic nuclei also can occur during surgery, when the pituitary stalk is transected more dorsally because of the dimensions of the neoplasm or because of limited operating visibility, which may lead to disturbance of the hypothalamus when the surgeon is attempting to remove the last dorsal pituitary remnants.[2] Dogs with larger tumors also require a longer surgery and anesthesia time to completely remove all pituitary adenoma tissue. This can explain the positive correlation observed in our study between persistent diabetes insipidus and anesthesia and surgical time. Surprisingly, no significant correlation was found between persistent diabetes insipidus and survival time or disease-free interval. Dogs with enlarged pituitary glands have a higher rate of recurrence because of the higher probability of leaving remnants of tumor tissue.[12] However, in our study, the presence of the persistent diabetes insipidus, frequently observed after the removal of enlarged pituitary glands, was not associated with shorter survival or higher rate of recurrence.

The postoperative mortality rate (10.2%) was the same as reported in a previous study,[12] whereas the recurrence rate appears to be less than previously reported (11.3% in the present study versus 27% in a previous study).[15] This is likely because of a different subset of patients included in both studies and possibly shorter follow-up time in our study.

The main limitations of our study are its retrospective design and some missing data (eg, duration of anesthesia and surgery in some patients, possible complications that were not recorded, distinction between prolonged or permanent diabetes insipidus). Moreover, a precise comparison between our study and previous studies is difficult and should be done with caution because of differences in electrolyte monitoring and the changes made over time to the postoperative IV fluid therapy protocol.

5 | CONCLUSION

Hypernatremia remains the most frequent electrolyte imbalance after transsphenoidal hypophysectomy, although a lower frequency was observed in comparison to previous reports. No associations with clinical or surgical variables were identified that could help to identify patients more at risk of severe hypernatremia. In our population, electrolyte imbalances were not associated with worse postoperative outcome.

The postoperative fluid protocol should be tailored to the individual patient's needs to prevent severe electrolyte imbalances. The survival and recurrence rates obtained in our study reflect ongoing experience and collaboration among the endocrinology, surgery, anesthesia, and intensive care units involved in the care of dogs undergoing hypophysectomy.

ACKNOWLEDGMENT

No funding was received for this study.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Sara Del Magno https://orcid.org/0000-0002-2900-6989
Björn P. Meij https://orcid.org/0000-0002-0165-1169

REFERENCES

1. Pivonello R, De Leo M, Cozzolino A, et al. The treatment of Cushing's disease. *Endocr Rev*. 2015;36:385-486.
2. Hanson JM, Hoofd MM, Voorhout G, et al. Efficacy of transsphenoidal hypophysectomy in treatment of dogs with pituitary-dependent hyperadrenocorticism. *J Vet Intern Med*. 2005;19:687-694.
3. Del Magno S, Fracassi F, Grinwis GCM, et al. Sequential treatment of a large corticotroph neoplasm and associated neurological signs in a dog. *J Am Anim Hosp Assoc*. 2018;55:e552-e502.
4. Sanders K, Kooistra HS, Galac S. Treating canine Cushing's syndrome: current options and future perspective. *Vet J*. 2018;241:42-51.
5. Vlugt Meijer RH, Meij BP, van den Ingh TS, et al. Dynamic computed tomography of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. *J Vet Intern Med*. 2003;17:773-780.
6. Del Magno S, Grinwis GCM, Voorhout G, et al. Dynamic computed tomography of the pituitary gland using a single slice scanner in dogs with pituitary-dependent hypercortisolism. *Res Vet Sci*. 2016;107:42-49.
7. Meij BP, Voorhout G, van den Ingh TS, Hazewinkel HA, Teske E, Rijnberk A. Results of transsphenoidal hypophysectomy in 52 dogs with pituitary-dependent hyperadrenocorticism. *Vet Surg*. 1998;27:246-261.
8. Mamelak AN, Owen TJ, Bruyette D. Transsphenoidal surgery using a high definition video telescope for pituitary adenomas in dogs with pituitary dependent hypercortisolism: methods and results. *Vet Surg*. 2014;43:369-379.
9. Owen TJ, Martin LG, Chen AV. Transsphenoidal surgery for pituitary tumors and other sellar masses. *Vet Clin North Am Small Anim Pract*. 2018;48:129-151.
10. Meij BP, Voorhout G, van den Ingh TS, et al. Transsphenoidal hypophysectomy in beagle dogs: evaluation of a microsurgical technique. *Vet Surg*. 1997;26:295-309.
11. Kristof RA, Rother M, Neuloh G, Klingmüller D. Incidence, clinical manifestations, course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study. *J Neurosurg*. 2009;111:555-562.
12. Van Rijn SJ, Galac S, Tryfonidou MA, et al. The influence of pituitary size on outcome after transsphenoidal hypophysectomy in a large cohort of dogs with pituitary-dependent hypercortisolism. *J Vet Intern Med*. 2016;30:989-995.
13. Evans HE. The skeleton. In: Evans HE, ed. *Miller's Anatomy of the Dog*. 4th ed. Philadelphia: Saunders Company; 2012;122-218.
14. Galac S, Kooistra HS, Teske E, Rijnberk A. Urinary corticoid/creatinine ratios in the differentiation between pituitary-dependent hyperadrenocorticism and hyperadrenocorticism due to adrenocortical tumour in the dog. *Vet Q*. 1997;19:17-20.
15. Behrend EN, Kooistra HS, Nelson R, Reusch CE, Scott-Moncrieff JC. Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (small animal). *J Vet Intern Med*. 2013;27:1292-1304.
16. Kooistra HS, Voorhout G, Mol JA, Rijnberk A. Correlation between impairment of glucocorticoid feedback and the size of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. *J Endocrinol*. 1997;152:387-394.
17. Finkel MJJ, Zwaveling-Soonawala N, Walenkamp MJE, et al. Frequent occurrence of the triphasic response (diabetes insipidus/hyponatremia/diabetes insipidus) after surgery for craniopharyngioma in childhood. *Horm Res Paediatr*. 2011;76:22-26.
18. Kiram Z, Sheikh A, Momin SNA, et al. Sodium and water imbalance after sellar, suprasellar and parasellar surgery. *Endocr Pract*. 2017;23:309-317.
19. Janneck M, Burkhardt T, Rotermund R, Sauer N, Flitsch J, Aberle J. Hyponatremia after trans-sphenoidal surgery. *Minerva Endocrinol*. 2014;39:27-31.
20. Taoda T, Hara Y, Masuda H, et al. Functional and morphological changes in the hypothalamus-pituitary posterior lobe system after hypophysectomy in the dog. *J Vet Med Sci*. 2006;68:1-7.

How to cite this article: Del Magno S, van Rijn S, Azzariti S, Valtolina C, l' Ami J, Meij BP. Plasma sodium and potassium concentrations after hypophysectomy in dogs with corticotroph adenomas. *J Vet Intern Med*. 2022;36(1):39-48. doi:10.1111/jvim.16337

APPENDIX A: STEROFUNDIN ISO COMPOSITION

One thousand milliliters of solution contains:
Active substances:

Sodium chloride, 6.8 g
Potassium chloride, 0.3 g
Magnesium chloride hexahydrate, 0.2 g
Calcium chloride dehydrate, 0.37 g
Sodium acetate trihydrate, 3.27 g
Malic acid, 0.67 g

Electrolyte concentrations in mmol/L:

Sodium, 145.0
Potassium, 4.0
Magnesium, 1.0
Calcium, 2.5
Chloride, 127.0
Acetate, 24.0
Malate, 5.0

Excipients:

Water for injection
Sodium hydroxide

APPENDIX B: STEROFUNDIN BG COMPOSITION

One thousand milliliters of solution contains:

Active substances:

Sodium chloride 1.25 g
Potassium chloride 1.8 g
Sodium dihydrogen phosphate dehydrate 1.14 g
Magnesium chloride hexahydrate 0.51 g
Sodium lactate-solution 50% w/w 5.6 g (equivalent to 2.8 g sodium lactate)
Glucose monohydrate 55 g (equivalent to 50.0 glucose)

Electrolyte concentrations in mmol/L:

Sodium 53.7
Potassium 24.1
Magnesium 2.5
Lactate 25.0
Chloride 53.5
Phosphate 7.3

Excipients:

Hydrochloric acid
Water for injection