

PTH and ionized calcium evaluation in unilateral thyroidectomized cats*

Avaliação de cálcio ionizado e paratormônio em gatos submetidos a tireoidectomia unilateral

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Resumo

O objetivo deste estudo é avaliar as concentrações de cálcio ionizado e paratormônio intacto (iPTH) após a tireoidectomia com implantação da paratireoide em gatos hipertireoideos. Gatos hipertireoideos podem apresentar hipocalcemia por apresentarem distúrbio na homeostase de cálcio. A tireoidectomia pode levar a hipocalcemia pós-operatória, sendo, portanto, fundamental a mensuração dos níveis de cálcio antes da cirurgia em pacientes hipertireoideos. Dezesete gatos com hipertireoidismo com lobos cervicais palpáveis foram examinados e avaliados laboratorialmente para a cirurgia. Tireoidectomia unilateral com implantação da glândula paratireoide foi realizada. Hemograma completo, ureia, creatinina, fosfatase alcalina, alanino aminotransferase, fósforo, potássio e tiroxina total foram realizados antes e sete dias após a cirurgia. Amostras de sangue para avaliar cálcio ionizado e paratormônio intacto foram coletadas antes e nos dias 1, 2, 7, 15 e 21 após a cirurgia. Os níveis séricos de cálcio diminuíram significativamente em 24 horas após a cirurgia. Hipocalcemia subclínica ocorreu em dois gatos. As concentrações de iPTH foram uniformemente baixas ao longo do estudo e não avaliaram a função da glândula paratireoide após a tireoidectomia nesses gatos. Não houve correlação entre os níveis de cálcio e de iPTH. Os resultados deste estudo sugerem que os níveis de iPTH não indicam função da glândula paratireoide e que os níveis de cálcio devem ser avaliados antes da tireoidectomia, mesmo nos casos de tireoidectomia unilateral.

Palavras-chave: calcemia, gatos, hipertireoidismo, paratireoide.

Abstract

The aim of this study was to measure ionized calcium and intact parathormone concentrations after unilateral thyroidectomy with parathyroid autotransplantation in hyperthyroid cats. Hyperthyroid cats may have calcium homeostasis disorder and have decreased calcium concentration. Calcium levels decrease after thyroidectomy and their levels must be measured before thyroidectomy. Seventeen hyperthyroid cats with palpable nodules were submitted to clinical and laboratorial examination and they were prepared to surgery. Unilateral thyroidectomy with parathyroid gland autotransplantation was performed. Concentrations of serum urea, creatinine, alkaline phosphatase, alanine aminotransferase, phosphorus, potassium, total thyroxine and hematologic profile were determined before and seven days after surgery. Blood samples for serum ionized calcium concentration were collected before and after surgery on days 1, 2, 7, 15, 21. Serum calcium concentration fell significantly in all cats within 24 hours after surgery. Hypocalcemia occurred in two cats without clinical signs. The iPTH concentration measurements for samples throughout the study were uniformly low, with no patterns or trends identified. There wasn't correlation between serum calcium levels and iPTH levels in any moment before and after surgery. iPTH couldn't indicate parathyroid gland function after thyroidectomy in cats. The results of this study suggest that calcium concentration of all thyroidectomized cats must be measured before surgery even if they are submitted to unilateral thyroidectomy. iPTH concentration doesn't evaluate parathyroid gland function.

Keywords: calcemia, cats, hyperthyroidism, parathyroid.

Introduction

Hyperthyroidism is the most common endocrine disease in cats and usually caused by adenoma or hyperplasia (Naan et al., 2006). Thyroidectomy is a definitive treatment when radioactive iodine is not available. Its most important complication is postoperative hypocalcemia because the parathyroid gland could be damaged or removed during the surgery (Flanders et al., 1991; Padgett et al., 1998). The parathyroid glands secrete parathyroid hormone

that it is responsible for the regulation of extracellular fluid calcium concentration. In human being, intraoperative intact parathyroid hormone is used to indicate parathyroid function during thyroidectomy (Quiros et al., 2005), but it is not available for animals. Hyperthyroid cats may have calcium homeostasis disorder and thyroidectomy decreases calcium concentrations postoperatively. Ionized calcium and parathormone concentrations should be evaluated before and after thyroid surgery to avoid postoperative hypocalcemia in hyperthyroid cats.

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The aim of this study was to measure ionized calcium and intact parathormone concentrations before and after unilateral thyroidectomy with parathyroid autotransplantation in hyperthyroid cats.

Materials and methods

Seventeen hyperthyroid cats with palpable thyroid gland were submitted to clinical and laboratory examination. They were stabilized to surgery with methimazole or atenolol to minimize the risk of anesthesia. Starting doses of methimazole range from 1.25 mg per cat to 2.5 twice daily. Higher doses of 5 or 7.5 mg per cat twice daily were introduced in cases of high serum T_4 concentration even after initial therapy. Atenolol 6.25 mg per cat once daily was introduced to cats with adverse reaction to methimazole (vomiting, anorexia). Scintigraphy was not available for Brazilian pets. After clinical and medical stabilization, cats were anesthetized according to clinical evaluation and concurrent medical problems. After endotracheal intubation, anesthesia was maintained with isoflurane in oxygen. Surgical technique employed was unilateral extracapsular thyroidectomy with transplantation of the parathyroid gland within the sternohyoid muscle (Norsworthy 1995). The myotomy was closed with nylon 4-0 to mark the site. Postoperatively tramal (1.0 mg/kg body weight, BID, subcutaneously, for three days) was administered for analgesia. The excised thyroid and the sample of parathyroid gland were examined histologically. Blood samples were collected by jugular venepuncture to hematologic, biochemistry (urea, creatinine, alkaline phosphatase, alanine aminotransferase, potassium, ionized calcium), intact parathyroid hormone (iPTH) and total thyroxine analysis. To serum ionized calcium measurement, blood without anticoagulant was immediately centrifuged. Ependorf was completely filled with serum and was kept at 0 to -20°C to be processed within three days. Serum sample with pH below 7.1 or above 7.4 was eliminated. The technique used was selected electrode method. The PTH concentration was measured using chemoluminescence for intact parathormone (iPTH). All samples were stored at -20°C to be processed within seven days.

Serum ionized calcium and intact parathormone concentrations were measured before and after surgery on days 1, 2, 7, 15, 21 of the study. Concentrations of serum urea, creatinine, alkaline phosphatase, alanine aminotransferase, phosphorus, potassium, ionized calcium, total thyroxine and hematologic profile were determined preoperatively and on day 7 postoperatively. When total thyroxine concentration was normal on day 7 postoperatively, a new sample was collected after six months to evaluate recurrent disease.

Wilcoxon Test was used to evaluate differences between the blood tests before and seven days after surgery. Comparison of parameters of serum ionized calcium concentration between pre-surgical time (pre-surg), 24 hours (24h), 48 hours (48h) 7 days (7d), 15 days (15d), and 21 days (21d) after surgery, as well as the comparison of iPTH and the same time, were made by the Friedman test or two-way ANOVA by Friedman Ordinances, followed by the Wilcoxon test to verify that the moments show significant differences between them. To verify the existence of correlation between the calcium and iPTH in the moments before and after surgery was performed Spearman correlation test. Mann-Whitney test was used to compare calcium concentration

median between cats with and without parathyroid gland transplantation. Spearman test was used to find postoperative correlation between biochemistry profile and total thyroxine concentration. The level of significance was considered to be $\alpha \leq 0.05$.

The study was approved by the Ethical Committee for Animal Experimentation at the Universidade Federal Fluminense and CEPA (Registro N^o 0095-09) and permission for participation of each cat was obtained from owners.

Results and discussion

There were nine castrated males and eight spayed female cats in age ranging from 9 to 19 years (mean age 13.5 years) and weight ranged from 2.290 to 5.320 (mean 3.8 kg). Hyperthyroidism is very common among older cats (Naan et al., 2006; Wakeling et al., 2011). Thirteen cats were Brazilian domestic short hair and four were siamese. The predominant breeds are domestic short-haired (Wakeling et al., 2011). Thyroid palpable cervical nodule was unilateral in eight cats and bilateral in nine cats. Bilateral thyroid lobe enlargement is more common in hyperthyroid cats (Peterson et al., 2015). Of the 16 cats in which echocardiogram evaluation was realized, 14 had cardiac abnormalities. About 37% of the hyperthyroid cats have one or more echocardiographic variable(s) outside the calculated normal range (Weichselbaum et al., 2005).

Preoperative creatinine was increased in two cats (2.0 and 2.1 mg/dL; reference: 0.5-1.9 mg/dL), nevertheless the owners opted for surgery because they could not medicate their cats. Serum creatinine increases in azotemic patients after hyperthyroidism control and indication for definitive treatment should be reevaluated. Successful treatment of hyperthyroidism decreases renal excretory function, resulting in an increase in the serum creatinine concentration and a decrease in the glomerular filtration rate. (Bichard, 2006, Riensche et al., 2008; Williams et al. 2010). 26,4% (Williams et al., 2010) to 51% (Riensche et al., 2008) of hyperthyroid cats developed renal insufficiency within 2 weeks to 6 months after hyperthyroidism treatment. Renal functional must be monitored closely in cats after hyperthyroidism treatment. Seven days after surgery these two cats had creatinine levels decreased (1.7 and 1.3 mg/dL; reference: 0.5-1.9 mg/dL), but the thyroxine levels were high (107 and 30.3 mg/dL; reference: 15-30 ng/dL) and for this reason creatinine levels didn't increase.

Serum potassium preoperative concentration was decreased in five cats. Serum alkaline phosphatase and alanine aminotransferase was increased in three and twelve cats, respectively. Total thyroxine levels ranged from 2.8 to 128.9 ng/mL (\bar{X} = 57.00 ng/mL \pm 39.04, reference: 15-30 ng/mL). Hepatic enzymes increase in hyperthyroid cats (Walkeling et al., 2011) and probably such abnormalities occur by direct toxic effects of thyroid hormones on the liver.

The reasons for surgery included adverse effects of methimazole (8/17 cases), difficulty in medicating and owners interest in surgical treatment (6/17 cases) and inability to stabilize with medical management (3/17 cases). That was similar to Harvey et al. (2009).

Hyperthyroidism is the most common endocrine disease in cats. Definitive management options include radioiodine therapy or

thyroidectomy (Bichard et al., 1984; Bichard, 2006; Naan et al., 2006; Harvey et al., 2009; Hibbert et al., 2009). In Rio de Janeiro, radioiodine therapy is not available, and thyroidectomy is the only option for definitive therapy for hyperthyroid cats.

None of the hyperthyroid cats died during 21 days after surgery. None developed any anesthetic or postoperative complications. Complications associated with surgical treatment of hyperthyroidism in cats may arise from disease itself, anesthesia, surgery or postsurgical management. Cats with hyperthyroidism have a higher relative risk of experiencing adverse events while undergoing to anesthesia (Bichard et al., 1984). Therefore, these cats must be stabilized with medication (methimazole or β -adrenoceptor blocking agents) before surgery to prevent anesthetic complications (Caney, 2013; Naan et al., 2006; Trepanier, 2006). In this report, the cats didn't have any anesthetic complication probably because they were stabilized with medication before surgery. Other complications as recurrent laryngeal nerve or vessel damage may occur (Naan et al., 2006; Radlinsky, 2007) but they weren't observed in this study as well.

The most serious complication of thyroidectomy is postoperative hypocalcemia which is commonly observed when bilateral thyroidectomy is performed (Flanders et al., 1987; Naan et al., 2006; Padgett et al., 1998). Staging thyroidectomies reduce or prevent the incidence and duration of postoperative hypocalcemia (Flanders et al., 1987; Norsworthy, 1995). Thyroidectomy with parathyroid gland transplantation on staged prevents postoperative hypocalcemia, hospitalization, and further oral supplementation of calcium and calcitriol because transplanted parathyroid tissue returns to its normal function within 21 days of surgery (Norsworthy, 1995; Padgett et al., 1998). For this reason, this surgery technique was chosen in this report. If these cats returned to hyperthyroidism after unilateral thyroidectomy, they could be submitted to contralateral thyroidectomy without developing hypocalcemia postoperatively.

Serum calcium concentration significantly fell in all cats within 24 hours after surgery (Figure 1). Hypocalcemia occurred in two cats without clinical signs (calcium levels: 1.04 and 1.02 nmol/L; reference: 1.07-1.5 mmol/L). Calcium concentration on first and second day after surgery were significantly lower than preoperative concentrations for all cats ($p = 0.01$ and $p = 0.02$, respectively). This is very important because hyperthyroid cats may have a significant derangement of calcium homeostasis, which results in low ionized calcium concentrations even before surgery (Barber and Elliott, 1992; Williams et al., 2013). This could be a potential risk for developing clinical hypocalcemia after unilateral thyroidectomy which is life threatening. Serum calcium concentration must be measured in all hyperthyroid cats before and after thyroidectomy.

There was no significant difference between preoperative calcium concentrations and calcium concentrations measured on days 7, 14 and 21 after surgery ($p = 0.41$; $p = 0.33$; and $p = 0.41$, respectively). Calcium levels returned to normal levels within seven days.

Serum preoperative iPTH concentration was 5.3 picog/mL (range 2 to 14 picog/mL; reference: 0- 41 picog/mL). The iPTH concentration measurements for samples throughout the study were uniformly low, with no patterns or trends identified (Figure 2). There wasn't correlation between serum calcium levels and iPTH levels in any moment before and after surgery. It was expected to observe reduction decreased of iPTH concentrations as it was for ionized calcium levels like observed for Flanders et al. (1991).

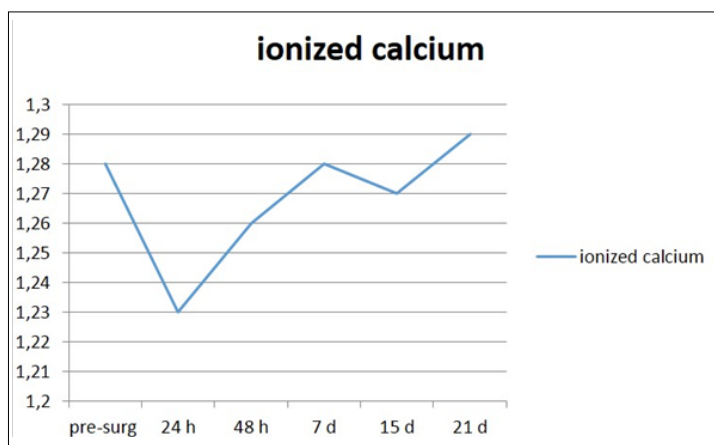


Figure 1: Ionized calcium mean before and within 21 after surgery of cats thyroidectomized

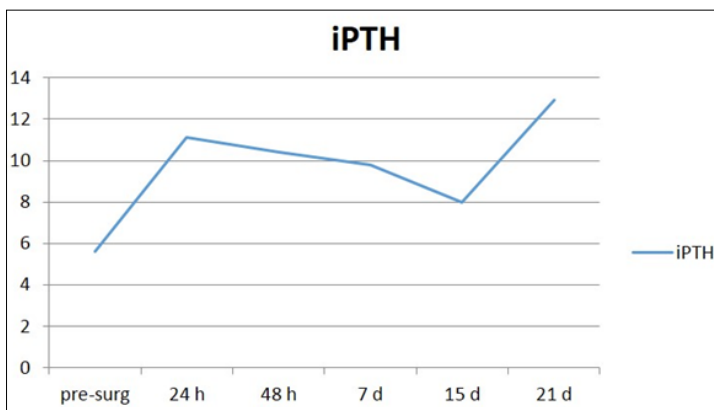


Figure 2: iPTH mean before and within 21 after surgery of cats thyroidectomized.

iPTH monitoring during thyroid surgery may identify patients at risks for hypocalcemia in the immediate postoperative period (Quiros et al., 2005; DiFabio et al., 2006; Julián et al., 2013). Intraoperative iPTH concentration could not be determined. iPTH concentration was determined before surgery and on first, second, seventh, fifteenth and twenty first days postoperatively. Significant change was not evident in iPTH concentration on these periods. iPTH should have decreased through 24 hours postoperatively (Julián et al., 2013) and should increase at 15 to 21 days postoperatively. This time parathyroid gland transplanted returned its function (Padgett et al., 1998). It was not observed in this study. iPTH concentrations were uniformly low throughout the study, but calcium levels decrease after surgery and begin to increase on seventh day postoperatively.

One reason could be that unilateral parathyroidectomy allowed function of contralateral parathyroid gland and its hormonal production and iPTH levels did not decrease. But if it was truth, calcium levels didn't have decreased after unilateral thyroidectomy either. Other explanation could be accommodation of existing calcium-regulating systems that operate at suboptimal levels in the absence of PTH (Flanders et al., 1991; Padgett et al., 1998) or iPTH concentration did not evaluate parathyroid gland function in cats and more studies are necessary to evaluate PTH function in thyroctemized cats.

The major concern of the chosen surgery technique was the difficulty in parathyroid gland identification. Parathyroid gland autotransplantation was performed in only 10 cats because it was not visible in the other seven cats. Norsworthy (2005) transplanted parathyroid gland of all thyroidectomized cats with no difficulty. Lack of experience may affect the identification of the parathyroid gland.

There was no difference in ionized calcium concentrations between cats submitted to thyroidectomy with autotransplantation of parathyroid gland and without autotransplantation. There wasn't correlation between serum calcium levels and parathyroid gland implantation in all moments (24h p= 0.68; 48h p= 0.78; 7d p= 0.10; 15d p= 0.49; 21d p= 0.67).

Recurrence of hyperthyroidism after thyroidectomy is caused by hypertrophy of adenomatous tissue left at the surgery site, presence of ectopic hyperfunctional thyroid tissue or hypertrophy of contralateral thyroid gland (Welches et al., 1989; Naan et al., 2006; Harvey et al., 2009). In this study, hyperthyroidism recurred

in seven cats on day 7 and in four cats on sixth month suggesting that hypertrophy of contralateral thyroid gland led to relapse of disease. These cats should be submitted to contralateral thyroidectomy to treat hyperthyroidism. Four cats were euthyroid at the end of study. Two cats died within four months following study due to unrelated causes.

Hyperthyroidism associated with benign thyroid adenoma is the most frequently diagnosed endocrinopathy in feline geriatric patients (Naan et al., 2006; Wakeling et al., 2007). Thyroid carcinoma is considered rare (Naan et al., 2006; Hibbert et al., 2009). Histological examination results were available for 17 cats and adenoma was detected in all of them. In these cases, surgery may be curative.

The results of this study suggest that ionized calcium concentration must be measured before thyroidectomy in cats. Ionized calcium concentration decreased significantly in cats submitted to unilateral thyroidectomy, and may decrease below the reference value if preoperative serum calcium measurement is already low, which can be life threatening. iPTH measurement didn't have correlation with ionized calcium concentration and didn't evaluate parathyroid gland function in cats.

Conclusions

Hypocalcemia can be observed after unilateral thyroidectomy although it is subclinic. Ionized calcium concentration must be evaluation before thyroidectomy. iPTH levels are not a valuable tool in assessing parathyroid function after thyroidectomy in cats.

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