

Comparison of complications following tibial tuberosity advancement and tibial plateau levelling osteotomy in very large and giant dogs 50 kg or more in body weight

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Keywords

Canine cruciate ligament rupture, tibial plateau levelling osteotomy, tibial tuberosity advancement, surgical site infection, CCLR, TPLO, TTA

Summary

Objectives: To analyse and compare major complications in dogs ≥ 50 kg undergoing tibial tuberosity advancement (TTA) or tibial plateau levelling osteotomy (TPLO) for treatment of cranial cruciate ligament disease.

Methods: Medical records and radiographs of client-owned dogs (≥ 50 kg) treated for cranial cruciate ligament disease with either TTA or TPLO between January 2011 and November 2015 were reviewed. Ninety-one TTA cases and 54 TPLO cases met the study inclusion criteria. All complications within one year of surgery were recorded. Major complications were those requiring surgical revision or intervening medical therapy to resolve. Logistic regression analysis evaluated for

associations with major complication occurrence. Major complications were statistically compared between TTA and TPLO treatment groups.

Results: Incidence of major complications following TTA and TPLO surgery were 19.8% and 27.8%, respectively. Surgical site infection (SSI) was the single most common major complication following both TTA (15.4%) and TPLO (25.9%) surgery. There were no significant differences between TTA and TPLO treatment regarding the rate of SSI, surgical revision, or overall occurrence of major complications. Postoperative antibiotic therapy significantly reduced the risk of a major complication in all dogs ≥ 50 kg ($p = 0.015$; OR: 0.201; 95%CI: 0.055–0.737).

Clinical significance: Major complications occurred frequently following TTA and TPLO treatment of cranial cruciate ligament disease in dogs ≥ 50 kg. The increased chance for SSI should be considered and postoperative antibiotic therapy is recommended.

Introduction

Cranial cruciate ligament disease is a common condition of the canine stifle (1). Loss of a functional cranial cruciate ligament generates excessive cranial tibiofemoral shear force during weight bearing, resulting in pelvic limb lameness and osteoarthritis development. Dynamic stabilization of the cranial cruciate ligament deficient stifle with either a tibial tuberosity advancement (TTA) or a tibial plateau levelling osteotomy (TPLO) is commonly performed (2–5). Each of these procedures utilize a tibial osteotomy to create a patellar (ligament) tendon angle (PTA) of $\sim 90^\circ$, which will effectively neutralize abnormal tibiofemoral shear force (6–8). Clinical outcome is favourable with both TTA and TPLO surgery (9–12).

Treatment of cranial cruciate ligament disease in very large and giant dogs can be clinically challenging. In separate reports, increasing body weight has been determined to be a risk factor for developing complications following both TTA and TPLO (13–16). Major complications are particularly concerning due to their associated patient morbidity and economic impact (17, 18). Major complications following TTA and TPLO have included implant failure, various fractures, surgical site infection (SSI), and delayed meniscal injury (13–15, 19–21). A recent investigation of dogs ≥ 50 kg treated by TPLO reported the development of SSI in 21.3% of cases (22). Similar studies investigating complications specific to very large and giant dogs following TTA are lacking.

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Table 1 Criteria for diagnosing surgical site infection (SSI) (27).

	Superficial incisional SSI	Deep incisional SSI	Organ/space SSI
Timing	≤30 days	≤30 days or 1 year with implant	≤30 days or 1 year with implant
Location	Skin or subcutaneous tissues of the incision	Deep soft tissues (fascia, muscle) of the incision	Any area manipulated during surgery other than incision
Clinical aspects*	<ul style="list-style-type: none"> • Positive bacterial culture • Purulent discharge • Presence of pain, localized swelling, and/or heat • Incision deliberately opened by surgeon unless cultured negative 	<ul style="list-style-type: none"> • Positive bacterial culture • Purulent discharge from deep incision but not organ/space • Deep incisional dehiscence • Abscess formation or other evidence of infection (fever, pain, swelling) • Incision deliberately opened by surgeon unless cultured negative 	<ul style="list-style-type: none"> • Positive bacterial culture • Purulent drainage from drain placed into the organ/space • Abscess or other evidence of infection on direct exam, during re-operation, histopathology, or radiology • Diagnosis of organ/space SSI by clinician

* One or more must be present.

Initially, the TTA procedure was limited to a maximum tuberosity advancement of 12 mm, and was not as applicable to very large and giant dogs (2, 23, 24). Inadequate tuberosity advancement may increase the risk for complication as well as affect clinical outcome (15). Since these earlier reports, larger advancement cages (16 mm^a and 15 mm^b) have been made commercially available, allowing surgeons to more readily achieve a PTA of 90° in larger dogs. Furthermore, no studies have attempted to directly compare major complications following TTA and TPLO surgery in dogs ≥50 kg to determine if either procedure should be preferred for minimizing major complication occurrence.

The purpose of this study was to describe complications in dogs ≥50 kg following TTA and TPLO surgery for cranial cruciate ligament disease, and to analyse and compare major complications within and between these two treatment options. We hypothesized there would be no significant difference in major complications following TTA and TPLO surgery in dogs ≥50 kg.

Materials and methods

Inclusion criteria

Medical records were retrospectively reviewed from January 2011 to November

2015. Cases were included with the following criteria: 1) diagnosis of unilateral cranial cruciate ligament disease; 2) TTA or TPLO treatment; 3) body weight ≥50 kg at the time of surgery; 4) a complete re-evaluation (physical and radiographic examination); and 5) owner follow-up greater than or equal to one year following surgery. Diagnosis of cranial cruciate ligament disease was based on physical examination findings (e.g., pain on hyperextension, periarthral fibrosis, positive tibial thrust) and radiographic findings (stifle effusion). Cases were excluded if previous stifle surgery was performed, concurrent stifle disorders were present (e.g., medial patellar luxation), or if the case lacked re-evaluation or owner follow-up. If a dog was treated for unilateral cranial cruciate ligament disease, and was re-presented for treatment of contralateral cranial cruciate ligament disease, only the initial procedure was included.

Pre-, peri- and postoperative care

Anaesthesia protocols typically consisted of opioid premedication, induction with propofol^c, and intra-operative inhalant anaesthesia. Regional epidural anaesthesia was also provided in all cases. Intra-operative cefazolin^d (22 mg/kg IV) was administered prior to skin incision and again every 90 minutes until completion.

All procedures were planned and performed as previously described by a board-certified surgeon or a resident under their direct supervision (25, 26). A caudomedial arthrotomy was performed in all cases. Torn medial menisci were debrided and all intact menisci were released using a mid-body technique. A single TTA implant system^e was used. Regular or broad 3.5 mm TPLO plates^a were used either exclusively or in combination with a 3.5 mm dynamic compression plate^a (“double plating”). All TTA and TPLO implants were composed of 316L stainless steel.

Overnight postoperative analgesia consisted of hydromorphone^f (0.05–0.1 mg/kg q4–6h IM). Dogs were generally discharged with instructions for the owner to administer oral tramadol^g (3–5 mg/kg q8–12h) and carprofen^h (2.2 mg/kg q12h or 4.4 mg/kg q24h), firocoxibⁱ (5 mg/kg q24h), or deracoxib^j (1–2 mg/kg q24h). Postoperative antibiotic therapy (cephalexin^k [22 mg/kg q8h]) was prescribed at surgeon discretion.

e XGEN “forkless” TTA system: Securos, Fiskdale, MA, USA

f Hydromorphone: Baxter Healthcare Corp, Deerfield, IL, USA

g Tramadol: Amneal Pharmaceuticals, Glasgow, KY, USA

h Carprofen (Rimadyl[®]): Pfizer Animal Health, New York, NY, USA

i Firocoxib (Previcox[®]): Merial, Duluth, GA, USA

j Deracoxib (Deramaxx[®]): Elanco Animal Health, Greenfield, IN, USA

k Cephalexin (Keflex[®]): Advancis Pharmaceutical Corporation, Germantown, MD, USA

a Securos, Fiskdale, MA, USA

b Kyon Veterinary Surgical Products, Boston, MA, USA

c Propofol: Abbott Animal Health, Abbott Park, IL, USA

d Cefazolin: Sandoz Inc, Princeton, NJ, USA

Postoperative instructions were identical for TTA and TPLO. Recommendations were for suture or staple removal at 10–14 days and re-evaluation by the operating surgeon six weeks following surgery. Strict activity restriction was recommended until the six-week re-evaluation. A mediolateral stifle radiograph was used to evaluate osteotomy healing at that time. Instructions for a gradual increase in activity over the next four weeks were provided if uncomplicated osteotomy healing was observed. Additional follow-up was only recommended if there was a concern regarding patient recovery or if the owner desired.

Data collection

Data collected included patient signalment, body weight, body condition, physical examination findings, duration of anaesthesia and surgery, surgical report including implants, use of postoperative antibiotic therapy, re-evaluation findings (examination and radiographic), and all complications less than one year from the date of surgery. Dogs were classified as overweight based on a body condition score ≥4 using a five-point scale or ≥7 using a nine-point scale.

Complications were defined as major or minor (17). Major complications were those that required surgical revision or medical treatment to resolve based on the standard of care. The diagnosis of SSI was made by clinical criteria defined by the Centers for Disease Control and Prevention (► Table 1) (27, 28). Minor complications did not require surgical or medical treatment to resolve. The owners of cases without a major complication at the last re-evaluation were contacted via telephone to confirm the absence of any major complication within one year of surgery.

Statistical analysis

Statistical comparison between the TTA and TPLO groups included: age, body weight, body condition, gender, limb, anaesthetic and surgical time, postoperative antibiotic therapy use, re-evaluation time, and complications. Complications of interest were all major, surgical revision, SSI, SSI

Table 2 Summary of statistical comparison between tibial tuberosity advancement (TTA) and tibial plateau levelling osteotomy (TPLO) treatment groups.

	TTA (n = 91)	TPLO (n = 54)	p-value
Baseline comparisons			
Age (years)	5.0 ± 2.2	4.4 ± 2.3	0.137
Weight (kg)	55.4 (50–90)	59.6 (50–96)	0.069
Overweight	44 (49.4%)	27 (50%)	0.862
Gender			0.961
• Male	62	37	
• Female	29	17	
Limb			0.987
• Left	49	29	
• Right	42	25	
Anaesthesia time (min)	105 (70–295)	130 (80–210)	<0.001*
Surgery time (min)	40 (20–105)	57.5 (30–105)	<0.001*
Postoperative antibiotic therapy	85 (93.4%)	34 (63%)	<0.001*
Re-evaluation (days)	44 (28–201)	53 (32–127)	0.002*
Complications			
All major complications	18 (19.8%)	15 (27.8%)	0.388
• Surgical revision	5 (5.5%)	0	0.157
• SSI	14 (15.4%)	14 (25.9%)	0.12
• SSI + concurrent postoperative antibiotic therapy	13 (15.3%)	6 (17.6%)	0.785
• Implant removal	4 (4.3%)	8 (14.8%)	0.057
All minor complications	13 (14.3%)	12 (22.2%)	0.221

Continuous data presented as mean ± standard deviation (normally distributed). Continuous data presented as median (range) (non-normally distributed). Categorical data presented as counts and %. *Significant at p < 0.05. SSI = surgical site infection.

while receiving postoperative antibiotic therapy, implant removal, and all minor. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed data were reported as mean (± standard deviation) and compared with two sample t-test, and non-normally distributed data were reported as median (range) and compared with Mann-Whitney *U* test. Categorical data were compared with Fishers exact test (any cell count <10) or chi-square test. Variables within the TTA and TPLO groups were evaluated by logistic regression analysis for association with all major complications, SSI, and surgical revision. Odds ratio (OR) with 95% confidence intervals (CI) were reported. Logistic regression analysis of all cases was performed to evaluate if treat-

ment (TTA or TPLO) was associated with major complication occurrence. All statistical analysis were performed using a software program¹ with significance set at p < 0.05.

Results

TTA and TPLO groups

Ninety-one TTA cases from 21 separate breeds were included. The most represented breeds were Mastiff (n = 18), Rottweiler (n = 11), Newfoundland (n = 11), German Shepherd (n = 8), and Labrador Retriever (n = 8). Sixty-two dogs were

¹ SAS Version 9.4: SAS Institute Inc., Cary, NC, USA

Table 3 Logistic regression analysis of variables for association with major complication following tibial tuberosity advancement surgery.

Variable	Odds ratio	95% CI		p-value
		Lower limit	Upper limit	
Age	0.929	0.696	1.239	0.615
Weight	1.08	1.015	1.061	0.016*
Overweight	0.569	0.159	2.036	0.386
Anaesthesia time	1.003	0.982	1.024	0.782
Surgery time	1.019	0.979	1.061	0.361
Postoperative antibiotic therapy	0.308	0.021	4.444	0.387
Cage size (12 versus 16)	1.326	0.318	5.53	0.699

*significance at $p < 0.05$.

male (61 neutered; 1 intact) and 29 were female (28 spayed; 1 intact). The left and right stifles were affected in 49 and 42 cases, respectively. Mean age at the time of surgery was five years (± 2.2 years) and median body weight was 55.4 kg (range: 50–90 kg). Forty-four dogs (49.4%) were considered overweight. Body condition scores were not available in two cases.

Fifty-four TPLO cases from 18 separate breeds were included. The most represented breeds were Mastiff ($n = 12$), Rottweiler ($n = 6$), Newfoundland ($n = 5$), Labrador Retriever ($n = 5$), and Saint Bernard ($n = 4$). Thirty-seven dogs were male (34 neutered; 3 intact) and 17 dogs were female (16 spayed; 1 intact). The left and

right stifles were affected in 29 and 25 cases, respectively. Mean age at the time of surgery was 4.4 (± 2.3) years and median body weight was 59.6 kg (range: 50–96 kg). Twenty-seven dogs (50%) were considered overweight. The body condition score was not available in one case.

Median anaesthetic times for TTA and TPLO cases were 105 minutes (range: 70–295 min) and 130 minutes (range: 80–210 min), respectively. Median surgical times for TTA and TPLO cases were 40 minutes (range: 20–105 min) and 57.5 minutes (range: 30–105 min), respectively. Anaesthetic and surgical times for TTA procedures were significantly less than TPLO ($p < 0.001$) (► Table 2). In the TTA

cases, no intra-operative complications were reported. Cage size included 16 mm ($n = 55$), 12 mm ($n = 33$), 10.5 mm ($n = 1$), and 9 mm ($n = 2$). In the TPLO cases, two intra-operative complications were reported; one case had an intra-articular screw that was replaced, and one case had rotational subluxation during range of motion which was resolved by placement of an extracapsular lateral fabellar suture prior to closure. Implants included regular ($n = 13$) and broad ($n = 41$) plates. Six cases were double plated. Postoperative antibiotic therapy was prescribed in 85 (93.4%) and 34 (63%) of TTA and TPLO cases, respectively.

Median final in-hospital re-evaluation for all cases was performed 46 days (range: 28–201 days) after surgery. Final re-evaluation of TPLO cases was significantly later than TTA cases ($p = 0.002$) (► Table 2).

Complications

For the 91 TTA cases, 18 (19.8%) had a major complication which included SSI ($n = 14$), tibial tuberosity fracture ($n = 4$), and a tibial metaphyseal fracture. One case had concurrent tibial tuberosity fracture and SSI. Body weight was significantly associated with major complication occurrence ($p = 0.016$) (► Table 3). Median time of surgical revision was 13 days (range: 5–153 days) following surgery. All fractures progressed to radiographic union after open reduction and internal fixation. No variables were associated with surgical revision. The median time of SSI diagnosis was 20.5 days (range: 9–238 days) following surgery. Positive bacterial culture was obtained in 13 SSI cases (92.9%) (► Table 4). Definitive resolution of SSI required implant removal in four cases. Increasing body weight was significantly associated with the development of SSI ($p = 0.016$; OR: 1.088; 95%CI: 1.016–1.166). Thirteen TTA cases (13.2%) had minor complications, which included seroma formation ($n = 7$), minimally displaced tibial tuberosity fracture ($n = 3$), radiographic patellar ligament desmitis, incidental plate breakage, and incomplete incisional dehiscence.

For the 54 TPLO cases, 15 (27.8%) had a major complication which included SSI ($n = 14$) and one implant failure. In two cases

Microorganism	TTA	TPLO
Staphylococcus spp.		
• Staphylococcus pseudintermedius	-	3
• MDR Staphylococcus pseudintermedius	5	4
• Other Staphylococcus spp.	-	2
• Other MDR Staphylococcus spp.	3	1
Pseudomonas spp.	3	3
Escherichia spp.	-	1
Serratia spp.	1	-
Streptococcus spp.	1	-
Enterococcus spp.	1	-
Enterobacter spp.	1	-

Mixed bacterial culture results were obtained in some cases. MDR = multi-drug resistant.

Table 4 Summary of microorganisms cultured for the diagnosis of surgical site infection following tibial tuberosity advancement and tibial plateau levelling osteotomy surgery.

with SSI, concurrent fibular fracture was present. Postoperative antibiotic therapy was significantly associated with reducing major complications ($p = 0.009$) (► Table 5). The one case of implant failure occurred 22 days following surgery and progressed to radiographic union with prolonged external coaptation. The median time of SSI diagnosis was 15 days (range: 5–280 days) following surgery. Positive bacterial culture was obtained in 13 SSI cases (92.9%) (► Table 4). Definitive resolution of SSI required implant removal in eight cases. Postoperative antibiotic therapy was significantly associated with reducing SSI ($p = 0.021$; OR: 0.141; 95%CI: 0.027–0.746). Twelve TPLO cases (22.2%) had minor complications, which included seroma formation ($n = 7$), incisional irritation ($n = 2$), fibular fracture ($n = 2$), and incidental screw loosening.

Direct comparison of major complications following TTA and TPLO surgery found no significant differences regarding the development of SSI, surgical revision, or the overall occurrence of major complications (► Table 2). The most common complication for each group was SSI. Analysis of only TTA and TPLO cases receiving postoperative antibiotic therapy found no significant difference in the development of SSI.

Analysis of all dogs ≥ 50 kg (145 cases) did not find treatment selection (TTA or TPLO) to be associated with major complication occurrence. Postoperative antibiotic therapy was significantly associated with reducing the risk for major complication occurrence in all dogs ($p = 0.015$; OR: 0.201; 95%CI: 0.055–0.737).

Discussion

Major complications occurred frequently following TTA and TPLO treatment of cranial cruciate ligament disease in dogs ≥ 50 kg. In this study, major complications occurred in 19.8% and 27.8% of TTA and TPLO cases, respectively. These occurred most often in the perioperative period. The single most common major complication following TTA and TPLO surgery was SSI. There were no significant differences between TTA and TPLO regarding the rate of

Table 5 Logistic regression analysis of variables for association with major complication following tibial plateau levelling osteotomy surgery.

Variable	Odds ratio	95% CI		p-value
		Lower limit	Upper limit	
Age	0.733	0.512	1.048	0.089
Weight	0.956	0.877	1.041	0.303
Overweight	0.510	0.108	2.405	0.395
Anaesthesia time	1.00	0.961	1.041	0.99
Surgery time	1.007	0.948	1.069	0.824
Postoperative antibiotic therapy	0.108	0.02	0.587	0.009*
Double plate	3.807	0.366	39.586	0.263

*Significance at $p < 0.05$.

SSI, surgical revision, or the overall occurrence of major complications. As a result, neither procedure can be recommended as superior to the other for minimizing major complication occurrence in dogs ≥ 50 kg.

This study is the first to describe major complications specific to dogs ≥ 50 kg following TTA since the introduction of advancement cages > 12 mm. The major complication rate of 19.8% reported here is higher than previously described in cohorts of predominately medium to large sized dogs (14, 15, 23, 29). Direct comparison to these previous studies is challenged though by differences in complication definitions and case follow-up. That said, prior TTA studies have suggested increasing body weight to be a risk factor for complication occurrence (14, 15). We identified increasing body weight as a risk factor for major complication occurrence in this study, and specifically the development of SSI. Other factors associated with SSI following TTA have included prolonged anaesthetic and surgical time (20).

Cadaveric biomechanical studies report that the necessary advancement to achieve a PTA of 90° in medium to large sized dog ranges from 10.2–14.6 mm (30, 31). Intuitively, very large and giant dogs (≥ 50 kg) should require larger advancements, and in this study a 12 or 16 mm cage was used in 96.7% cases. We did not find any difference between the 12 mm and 16 mm advancement on major complication occurrence. A previous study reported increased complications in dogs advanced only 6 or 9 mm when compared to 12 mm (15). The lack of

significant effect in our study was interrupted as being due to appropriate preoperative planning and cage selection within our TTA population. We suggest practices that perform TTA in dogs ≥ 50 kg have larger cage sizes readily available.

Complications specific to TPLO in dogs ≥ 50 kg have been described, with a high rate of SSI reported (22). The results of our study are similar with SSI diagnosed in 25.9% of TPLO cases. A smaller sample size and the use of non-locking TPLO plates probably influenced our rate of SSI. Locking TPLO plates have been associated with reducing SSI in dogs ≥ 50 kg (22). Based on our rate of SSI with all non-locking plates, surgeons should consider the use of locking TPLO plates in all dogs ≥ 50 kg. Postoperative antibiotic therapy was also found to significantly reduce the risk of SSI in dogs ≥ 50 kg. This is consistent with previous studies (13, 22, 32). No conclusions could be made regarding the direct effect of postoperative antibiotic therapy on the rate of SSI following TTA due to the high number of TTA cases in this report which were prescribed postoperative antibiotic therapy. A previous study did not find postoperative antibiotic therapy to affect the rate of SSI following TTA (20). Importantly, the rate of SSI between TTA and TPLO cases receiving postoperative antibiotic therapy was similar.

The reason for increased risk of SSI in dogs ≥ 50 kg is unclear. Solano and colleagues proposed micromotion at the osteotomy from increased mechanical load as the cause. Instability during bone healing

was found to be associated with SSI in several orthopaedic studies (33–35). Improved stability with preservation of the local vascular network are benefits of locking implants (36–38). Traditionally, TPLO stability is dependent on dynamic compression plating, while TTA stability is dependent on a pin and tension band effect between the plate and pull of the patellar ligament. It was hypothesized that this difference may decrease the risk for SSI following TTA surgery (20). The rate of SSI following TTA in dogs ≥ 50 kg was not significantly less than TPLO. Provided the sample size of our study, a type II error cannot be excluded. However, if we extrapolate the data published by other authors (188 TPLO cases with 40 SSI), where inclusion criteria and SSI definitions were similar, the larger sample size in a chi-square model still does not result in a significant difference for the development of SSI when compared to our TTA group (22).

Surgical revision was uncommon following TTA, and was not required for any TPLO case. Surgical revision was necessary in only 5.5% of TTA cases, comparable to previous studies (14, 19, 23). Fracture of the tibial tuberosity was the most common reason for surgical revision in this report. One study investigating tibial tuberosity fracture associated various aspects of surgical technique with fracture occurrence, but it did not associate body weight with fracture occurrence (19). As such, TTA in dogs ≥ 50 kg can have a low rate of surgical revision so long as meticulous surgical technique is maintained. Tibial tuberosity fracture was recorded as a minor complication in three cases. In those cases, fractures were incidentally diagnosed on scheduled radiographic follow-up, with healing callus and minimal displacement of the tibial tuberosity, and minimal impact on clinical function. Similar presentation and conservative fracture management has been described previously (14, 39, 40).

Limitations inherent to the retrospective design of this study include a lack of randomization and a reliance on medical record accuracy. Despite this, the treatment groups were highly comparable with regard to age, weight and body condition, gender, and breeds. The difference in final re-evaluation was attributed to the smaller

sample size of the TPLO group coupled with longer follow-up for complication resolution (e.g. implant removal for SSI). The median re-evaluation of 46 days for all cases was equivalent to the routine six-week recommendation. Standard definitions were used for reporting complications and SSI (17, 27). This allows for direct comparison of our results to future studies utilizing similar definitions.

We performed long-term telephone follow-up in cases without a major complication to confirm accurate complication reporting. That said, retrospective studies may risk overestimating major complication occurrence. The owners of dogs experiencing routine recovery may be more likely to have the re-evaluation performed by the primary veterinarian and be lost to follow-up, while the owners of dogs that develop an unexpected lameness are often referred to the operating surgeon for re-evaluation. Due to this, prospective studies may find lower complication rates than those described here. Minor complications were not a primary focus in this study, as they can be variably recorded, resolve without therapy, and minimally affect clinical outcome.

In conclusion, dogs ≥ 50 kg have a high incidence of major complications, and specifically SSI, following TTA and TPLO treatment of cranial cruciate ligament disease. Major complications were not significantly different between these two procedures. Treatment recommendations should continue to be based on individual patient factors, surgeon preference, and experience. Surgeons can reduce the risk for major complication in dogs ≥ 50 kg with postoperative antibiotic therapy.

Author Contributions

ECH was responsible for study conception, design and acquisition of data. MDB and SCK were responsible for study design. SJN was responsible for data acquisition and analysis. All authors were involved in the drafting or revising of the manuscript and have approved the final submitted version.

Conflict of interest

M. Barnhart is a paid lecturer for Securos and receives royalties from the sales of some of their products

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