Association of tibial plateau leveling osteotomy with proximal tibial osteosarcoma in dogs

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OBJECTIVE

To assess for any association between a history of tibial plateau leveling osteotomy (TPLO) and subsequent development of proximal tibial osteosarcoma in dogs.

DESIGN

Matched case-control study.

ANIMALS

34 client-owned dogs in which proximal tibial osteosarcoma was diagnosed between January 2005 and December 2012 (cases) and 79 dogs without osteosarcoma, matched 3:1 to cases (when possible) by age, breed, and initial examination date (controls).

PROCEDURES

Information on each case and control was collected from the medical records and other sources regarding date of birth, sex and neuter status, body weight, breed, and whether TPLO had been performed ≥ 1 year ago. A multivariable conditional logistic regression model was constructed to evaluate associations of body weight and history of TPLO with the outcome of proximal tibial osteosarcoma in dogs.

RESULTS

After adjusting for body weight in the multivariable model, dogs with a history of TPLO were 40 times as likely to develop proximal tibial osteosarcoma as were dogs with no history of TPLO. In addition, each 1-kg (2.2-lb) increase in body weight was associated with an 11% increase in the odds of proximal tibial osteosarcoma.

CONCLUSIONS AND CLINICAL RELEVANCE

Results suggested that dogs with a history of TPLO were at increased risk of developing osteosarcoma of the proximal region of the tibia relative to dogs with no such history. Therefore, it is important for proximal tibial osteosarcoma to be included among the differential diagnoses for new or worsening hind limb lameness in dogs that underwent TPLO ≥ 1 year previously. (*J Am Vet Med Assoc* 2018;253:752–756)

Sarcoma development following orthopedic fixation is a rare and devastating complication in dogs and people.[1,2] Sarcomas can arise in the bone or soft tissues at the site of a previous fracture or in the region of a fracture fixation implant between 9 months and 15 years (mean, 6 years) after fixation surgery.[3,4] Several proposed mechanisms for tumor development exist. One theory is that implant corrosion and resultant accumulation of metal debris in the region of the implant cause an altered host reaction with disrupted cellular activity, leading to cancer development.[2] Other theories include suggestions that an implant-associated infection alters cellular activity, that an implant acts as a nidus for persistent inflammation, and that any process causing long-term bone stimulation could result in sarcoma.[2]

ABBREVIATIONS

CI	Confidence interval
CSU-VTH	Colorado State University Veterinary Teaching Hospital
TPLO	Tibial plateau leveling osteotomy

Developed for treatment of cranial cruciate ligament rupture, the TPLO procedure involves a biradial osteotomy of the proximal tibial metaphysis and stabilization with placement of a specialized TPLO bone plate.[5] Since the procedure was introduced, there have been several reports[3,6–9] of sarcomas occurring at the TPLO site, with osteosarcoma being the most commonly reported tumor type. Although development of osteosarcoma at the TPLO site has been documented[10,a] to be a rare consequence of the procedure, to the authors' knowledge no studies have been conducted to evaluate whether TPLO actually increases a dog's risk of developing osteosarcoma at the site. The purpose of the study reported here was to assess for any association between a history of TPLO and subsequent diagnosis of proximal tibial osteosarcoma in dogs. The hypothesis was that dogs with proximal tibial osteosarcoma would have markedly increased odds of having undergone TPLO procedures in the past, compared with dogs without proximal tibial osteosarcoma.

Materials and Methods

A matched case-control study was performed by reviewing medical records of dogs evaluated at the CSU-VTH between January 1, 2005, and December 31, 2012. This type of study design was chosen because of the documented low incidence of osteosarcoma in dogs and the long period between TPLO procedure and osteosarcoma development (mean, 5.3 years).[6,10]

Animals

Case definition—An electronic search of an institutional primary tumor database was performed on June 1, 2013, to identify dogs with histologically confirmed proximal tibial osteosarcoma diagnosed within the study period. Potential cases were consecutively selected, and for inclusion, it had to be possible to determine (through CSU-VTH medical records, referring veterinarian records, or follow-up telephone conversation with owners) whether the dog had undergone ≥ 1 TPLO procedure anywhere at any point in the past. Dogs with osteosarcoma at a TPLO site were only classified as exposed (to TPLO) if the TPLO preceded the diagnosis of osteosarcoma by ≥ 1 year. The 1-year time frame was chosen because that is the reported[11] minimum latency for implant-associated sarcoma development in dogs. Assessment of eligibility for the case group was performed between June 1 and September 1, 2013.

Control definition—Medical records were searched to identify dogs evaluated at CSU-VTH within the study period for reasons other than diagnosis or treatment of osteosarcoma. Controls were selected this way in an effort to obtain a population of dogs similar to the case population and with owners of a similar socioeconomic status and motivation to treat more complex diseases in their dogs. For inclusion as a control, each dog had to have details available (within the CSU-VTH medical records, through the referring veterinarian, or by owner follow-up) regarding whether a TPLO procedure had been performed any time in the past at CSU-VTH or elsewhere. Dogs that developed osteosarcoma during the follow-up period or had a history of osteosarcoma were ineligible to be a control; however, dogs that developed or that had a history of other diseases or cancer types were not excluded. Just as for cases, assessment of eligibility for the control group was performed between June 1 and September 1, 2013.

Matching—The goal of a case-to-control ratio of 1:3 was chosen to maximize power of the analyses.[12] The criteria for matching controls to cases required that controls be the same breed as their matched case, differ from their matched case in age at initial examination by ≤ 2 years, and differ from their matched case in time of initial examination by ≤ 1 calendar year (to allow equal opportunity between groups for exposure to TPLO). When ≥ 3 possible controls were available for a given case, 3 controls were selected randomly from the available dogs by use of a random number list generated in commercially available spreadsheet software.[b]

Data collection

Information collected from medical records of cases and controls included date of examination at CSU-VTH, date of birth, sex and neuter status, body weight, breed, and whether TPLO had been performed previously. If a dog had previously undergone TPLO, then the approximate date of that procedure was recorded. Assessment of TPLO history involved review of medical records (eg, assessment of history forms, referring veterinarian records, and surgery reports) combined with interviews of owners and referring veterinarians. For controls only, information was also collected as to whether the dogs had received a diagnosis or treatment for osteosarcoma; for cases only, additional information was gathered pertaining to side (left or right) of the affected limb and whether the osteosarcoma was at the site of a previous TPLO.

Statistical analysis

Descriptive statistics were calculated for signalment characteristics of the case and control groups. A multivariable conditional logistic regression model was constructed with a backward stepwise procedure to evaluate associations between proximal tibial osteosarcoma (outcome variable) and history of TPLO (exposure variable). Other exposure variables considered for inclusion in the model were sex, neuter status, and body weight. The critical α value for retention of a given exposure variable was set at 0.05. First-order interactions between pairs of exposure variables included in the final model were evaluated. Odds ratios and associated 95% CIs were calculated from the final model. Statistical analyses were performed with statistical software.[c] Values of $P < 0.05$ were considered significant.

Results

A total of 113 dogs (34 cases and 79 controls) were included in the study **(Table 1)**. Spayed female dogs were common, representing 20 of the 34 (59%) cases and 32 of the 79 (41%) controls. Mean ± SD age at initial examination was 7.78 ± 2.94 years for cases and 7.60 ± 3.07 years for controls. Mean body weight at initial examination was 41.8 ± 14.1 kg (92.0 ± 31.0 lb) for cases and 36.0 ± 14.0 kg (79.2 ± 30.8 lb) for controls.

Variables retained in the final conditional logistic regression model were body weight and history of TPLO. After body weight was adjusted for, a dog with a history of TPLO was 40 times as likely to develop proximal tibial osteosarcoma as a dog with no history of TPLO (OR, 40.65; 95% CI, 4.04 to 409.06; $P = 0.002$). In addition, each 1-kg (2.2-lb) increase in body weight was associated with an 11% increase in odds of proximal tibial osteosarcoma (OR, 1.11; 95% CI, 1.03 to 1.20; $P = 0.005$). The interaction between

Table 1—Characteristics of dogs with (cases) and without (controls) proximal tibial osteosarcoma, stratified by whether they had a history of TPLO.

Characteristics	All cases (n = 34)	Cases with prior TPLO (n = 6)	Cases with no prior TPLO (n = 23)	All controls (n = 79)	Controls with prior TPLO (n = 6)	Controls with no prior TPLO (n = 73)
Sex and reproductive status						
Spayed female	20 (59)	7 (63.6)	13 (57)	32 (41)	1 (17)	31 (42)
Sexually intact female	0	0	0	1 (1.0)	1 (17)	0
Castrated male	14 (41)	4 (36)	10 (43)	41 (52)	4 (67)	37 (51)
Sexually intact male	0	0	0	4 (5)	0	4 (5)
Unknown	0	0	0	1 (1)	0	1 (1)
Age at initial examination (y)	7.78 ± 2.94	9.40 ± 2.32	7.01 ± 2.93	7.60 ± 3.07	6.28 ± 2.28	7.70 ± 3.12
Body weight (kg)	41.8 ± 14.0	47.5 ± 17.5	39.1 ± 11.5	36.0 ± 14.0	50.1 ± 17.1	34.9 ± 13.2

Data for sex and reproductive status are reported as number (%) of dogs, and data for age and body weight are reported as mean ± SD.

these 2 exposure variables was not significant (P = 0.92) when included in the final model.

Discussion

For the dogs of the present study, a history of TPLO performed ≥ 1 year previously was associated with significantly higher odds of developing proximal tibial osteosarcoma than for dogs with no history of TPLO. This population consisted of middle-aged large-breed dogs that typified those often treated with TPLO for cranial cruciate ligament rupture as well as those at risk of developing appendicular osteosarcoma. Although appendicular osteosarcoma can spontaneously arise within the proximal region of the tibia, this is uncommon,[13–16] and there are sporadic reports[3,6–9] of sarcoma development at the site of previous TPLO procedures in dogs. Despite the estimated incidence of TPLO-site osteosarcoma being reportedly low,[10,a] it is possible that factors associated with the TPLO procedure, as the findings of the present study suggested, could result in increased risk of osteosarcoma development given enough time following TPLO surgery. Further study is needed to determine whether these findings apply to other populations of dogs or have a biological basis.

In dogs, osteosarcoma development has been reported subsequent to fractures[4,11,17–20] and elective orthopedic procedures, including at the site of a cortical bone allograft,[21] total hip joint replacement,[22,23] triple pelvic osteotomy,[24] and tibial tuberosity advancement.[25] In humans, however, development of such sarcomas is considered rare and is only sporadically reported.[26,27] Different factors proposed to increase the risk of fracture-associated osteosarcoma include long-standing inflammatory reaction to the implant, surgical site infection, and implant corrosion.[2,18,26] Owing to the high risk of recall bias and lack of readily available information for all cases in the present study that could have resulted in important missing data, we did not assess for presence or lack of infection around the time of the TPLO procedure. A recent study[28] failed to find increased risk of osteosarcoma following open fracture repair, which suggested that infection at the surgical site may not have been a principal factor underlying the increased risk of osteosarcoma in dogs following TPLO.

Regarding corrosion of implants as a potential contributing factor, a report[8] of sarcoma development at the TPLO site in a dog includes histologic evidence of extra- and intracellular debris, presumed to be from the TPLO plate, and discusses the possibility of plate corrosion contributing to tumor development. Further assessment was performed to determine the composition of TPLO implants and whether they may have been less resistant to corrosion.[29] On the basis of metallurgic analyses on new and retrieved TPLO plates, that study[29] determined that the plates were manufactured with 316L stainless steel in a casting process, resulting in variability in chemical composition among plates and within regions of single plates. In addition, all 11 TPLO plates studied had residua, inclusions, and cavities that were absent in the dynamic compression plate analyzed.[29]

Additional studies[30,31] yielded conflicting findings with respect to documentation of corrosion of explanted TPLO plates. Concern was also raised that early TPLO plates manufactured through a casting process, versus being wrought, may have greater risk of implant corrosion, compared with the risk in wrought plates. In addition, the casted plates may have allowed instability of the fixation, potentially resulting in delayed union. In the present study, it was not possible to ascertain aspects of the TPLO plates (eg, identity of the plate manufacturers, compositions, or production processes) implanted in dogs that developed osteosarcoma; however, osteosarcoma has been documented[6,a] to have occurred at the site of TPLO with various plate manufacturers and implant materials.

The predominance of spayed female dogs in the present study was in contrast to a study[32] in which a greater number of male dogs than female dogs was observed and to another study[33] in which male dogs were at increased risk of osteosarcoma relative to female dogs. Heavier body weight was also associated with increased risk of osteosarcoma development at the proximal tibial site in the study reported here. These findings were contrary to those of previous reports[32,34] in which body size alone was not thought to

result in a greater risk of osteosarcoma development, although different breeds of similar body weight and body size have been reported[13,34,35] to have unequal incidences of osteosarcoma. In people, neither body weight nor height has been found to increase the risk of osteosarcoma development.[36–38] In the present study, the association between body weight and osteosarcoma risk could have been a unique finding because of factors (eg, long-term instability and delayed healing) that may have resulted in chronic inflammation in dogs following TPLO. Alternatively, body weight could have been a surrogate indicator of breeds with higher incidence of osteosarcoma, or this association could have been attributable to type I error.

Considerable effort was made in the present study to ensure that an accurate TPLO history and osteosarcoma status were obtained for each included dog; however, the possibility for inaccurate classification with respect to these variables remained to some degree. Medical records from referring veterinarians may have been incomplete regarding TPLO history and dogs consequently misclassified with respect to this exposure variable. Information ascertained from dog owners specifically could have introduced recall bias. Misclassification bias could also have existed if dogs in the control group had undiagnosed proximal tibial osteosarcoma at the time of inclusion. However, such an aggressive disease was likely to have been diagnosed during the medical record review process and the potential control therefore excluded. Dogs included in the case group could be reasonably assured to have had proximal tibial osteosarcoma because histologic confirmation following amputation was part of the case definition. Despite these possible limitations, there was evidence in the present study of an association between a history of TPLO and development of proximal tibial osteosarcoma in dogs that merits further investigation.

Acknowledgments

The authors acknowledge Jeffrey Neu for funding and support of this study.

The authors had no financial interests with companies that manufactured products that were the subject of the present research or with companies that manufactured competing products.

Footnotes

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b. Microsoft Excel for Mac 2011, version 14.6.2, Microsoft Corp, Redmond, Wash.
c. Stata, version 13, StataCorp LLC, College Station, Tex.

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From this month's *AJVR*

Effects of two levels of partial neuromuscular block with atracurium on the ventilatory response to hypercapnia in anesthetized Beagles

Daniel M. Sakai and Manuel Martin-Flores

OBJECTIVE
To evaluate effects of 2 levels of partial neuromuscular block on the ventilatory response to a hypercapnic challenge in anesthetized dogs and to evaluate effects of edrophonium for reversing partial neuromuscular block.

ANIMALS
6 healthy adult Beagles.

PROCEDURES
Each dog was anesthetized twice with propofol and dexmedetomidine. End-tidal partial pressure of CO_2 (P_{ETCO_2}), tidal volume (V_T), and peak inspiratory flow (PIF) were measured during breathing at rest. Maximal V_T and PIF ($V_{T_{MAX}}$ and PIF_{MAX}, respectively) in response to a hypercapnic challenge consisting of 10% CO_2 inhaled for 1 minute were measured. Variables were measured before administration of atracurium (baseline), during moderate (train-of-four [TOF] ratio, 0.3 to 0.5) and mild (TOF ratio, 0.6 to 0.8) atracurium-induced neuromuscular block, and after neuromuscular block recovery (TOF ratio, ≥ 0.9) after administration of edrophonium or saline (0.9% NaCl) solution. Dogs for which any variable returned to < 80% of the baseline value were identified.

RESULTS
Partial neuromuscular block increased P_{ETCO_2}; it impaired V_T at rest and $V_{T_{MAX}}$ but not PIF at rest and PIF_{MAX}. All variables except P_{ETCO_2} returned to baseline values when the TOF returned to ≥ 0.9. After recovery from neuromuscular block, significantly more dogs had a $V_{T_{MAX}}$ < 80% of the baseline value when edrophonium was not administered.

CONCLUSIONS AND CLINICAL RELEVANCE
Partial neuromuscular block in anesthetized Beagles decreased spontaneous ventilation at rest and impaired the response to a hypercapnic challenge. Response to hypercapnic challenge might remain partially impaired after recovery of the TOF ratio to ≥ 0.9. (*Am J Vet Res* 2018;79:915–920)

September 2018

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