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A Novel Approach to the Use of Animals in Studies of Pain: Validation of the Canine Brief Pain Inventory in Canine Bone Cancer

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Abstract

Objective—To validate the Canine Brief Pain Inventory (Canine BPI) which is based on the human Brief Pain Inventory (BPI), in a canine model of spontaneous bone cancer.

Design and Participants—100 owners of dogs with bone cancer self-administered the Canine BPI on 3 occasions to test the reliability, validity, and responsiveness of the measure.

Outcome Measures—Factor analysis, internal consistency, convergent validity, and an extreme group validation assessment were completed using the responses from the first administration of the CBPI. Test-retest reliability was evaluated using two administrations of the instrument, one week apart. Responsiveness was tested by comparing responses 3 weeks apart.

Results—The “severity” and “interference” factors hypothesized based on the BPI were demonstrated in the Canine BPI in dogs with bone cancer. Internal consistency was high (Cronbach’s alpha 0.95 and 0.93), as was test-retest reliability (kappa 0.73 and 0.65). Convergent validity was demonstrated with respect to quality of life (r=0.49 and 0.63). Extreme groups validation against normal dogs showed significantly higher factor scores (P<0.001 for both).

Conclusions—The Canine BPI reliably measures the same pain constructs in the companion canine model of spontaneous bone cancer as the BPI does in people with bone cancer. This innovative approach to preclinical outcomes development, validating a preclinical outcome measure that directly corresponds to an outcome measure routinely used in clinical research, applied to a readily available animal model of spontaneous disease could transform the predictive ability of preclinical pain studies.

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Conflicts of Interest: None

Keywords

bone cancer pain; outcomes; canine model

Introduction

Developing new therapies often requires testing in animal models to evaluate safety and efficacy before introduction into humans. Further, development of new treatments for veterinary use requires appropriate testing in animals to ensure safety and effectiveness. To the degree that naturally occurring diseases in companion animals (pets) mimic the same conditions in people, carefully studying new treatments in these animals has the potential to achieve human and veterinary goals in the same studies. In chronic pain research, studies in laboratory animals with experimentally induced pain have been only partially successful in predicting human clinical trial outcomes.(1–6) These experimentally induced conditions may not adequately model the natural disease process that leads to pain. The spontaneous pain caused by naturally occurring diseases in companion animals requires treatment for the animals' sake, and carefully studying novel therapies in these animals may provide greater insight into the potential efficacy in humans.

There is growing interest in using the diseases that spontaneously develop in companion dogs to investigate pharmaceutical efficacy, particularly in diseases with easily quantifiable endpoints.(7–16) Many of these animals will develop chronic pain due to the same conditions that afflict humans, such as bone cancer, which is the most common pain syndrome encountered in human cancer patients.(17,18)The assessment of chronic pain, however, has no gold standard objective measure in humans or animals. Therefore, before the study of response to therapy in dogs with chronic pain from naturally occurring disease can provide valuable insight into pharmaceutical efficacy for humans, valid and reliable outcome pain measures for use in companion dogs must be developed. While the initial development of owner based outcome assessments for companion dogs have been recently reported, none take the approach of basing the veterinary assessment on the human assessment to enhance the translational potential of the outcome measure.(19–21)

To take advantage of the extensive experience of pain measurement in humans for the development of an instrument for use in dogs, a widely accepted reliable and valid assessment of pain severity and interference with function, The Brief Pain Inventory (BPI) (22,23)was used as the basis for the Canine BPI (CBPI), which allows dog owners to quantify the severity and impact of their arthritic dog's pain.(24) If the CBPI can be generalized to canine bone cancer pain, it will be useful as an outcome measure of efficacy for the testing of novel compounds in these animals that have a disease that may mimic the human disease more closely than available experimental models. The results of such studies would be applicable to veterinary pharmaceutical development as clinical data and human pharmaceutical development as preclinical data. If results from the canine studies prove predictive of results in human clinical trials, using the CBPI in the companion canine model could help bridge the gap between basic preclinical and clinical human pain research (Table 1).

Methods

One goal in developing the Canine BPI (CBPI) was to preserve as much as possible the dimensional format, item structure and response scaling of the BPI, which has been widely validated in human studies. Given that the severity items are general in nature, widely used in both self- and observer-report paradigms, and accepted as a primary outcome for human

clinical trials, they were maintained unchanged. Therefore, like the BPI the CBPI contains 4 questions pertaining to the severity of the dog's pain, the responses to which can be used individually or averaged to deliver a pain severity score (Appendix 1). The pain interference items were constructed using the standard methodology for stepwise development of instruments designed to assess subjective states(25–30), and were initially developed in a group of companion dogs with osteoarthritis using factor analysis, reliability, and validity testing.(24) The response to these 6 questions pertaining to how the pain interferes with the dogs normal activities can be averaged to deliver a pain interference score. In addition a single global quality of life (QOL) question is included at the end of the questionnaire to obtain the owner's overall assessment of the dog's status.

In testing the reliability and validity of the CBPI in dogs with bone cancer, our hypotheses were that 1) the primary CBPI (i.e., not including the QOL question) is a two-factor questionnaire with a Cronbach's alpha > 0.70 for each factor; 2) the arithmetic mean of the items in the severity factor (severity score) and the impact factor (interference score) have good test-retest reliability between the first and second administrations of the instrument (κ>0.60) and are moderately correlated with the global QOL (i.e., $r > 0.4$); 3) severity and interference scores in dogs with bone cancer are significantly higher than those obtained in clinically normal dogs; and 4) severity and interference scores are responsive to change in the health status of the animal over time, significantly worsening between the first and third administrations of the instrument. The protocol was approved by the Veterinary Internal Review Board as well as the Institutional Animal Care and Use Committee.

These hypotheses were tested in a cohort of 100 owners of dogs with bone cancer who were recruited via flyer, newspaper, and radio ads. Following the written consent of owners, dogs were screened with a detailed history, physical examination, radiographs of the bones determined to be affected based on physical exam, complete blood count and biochemistry screen. For dogs to be eligible for the study, a veterinary radiologist confirmed the radiographic diagnosis of bone cancer, the dogs had no evidence of neurologic disease on physical exam, and blood work revealed no abnormalities that would require further diagnostics or the institution of therapy beyond the analgesics and anti-inflammatory drugs that dogs were already receiving (i.e., elevated blood glucose suggestive of diabetes mellitus, elevated blood urea nitrogen in the face of a normal creatinine suggesting gastrointestinal bleeding, etc.). If screening revealed such abnormalities, the dogs were referred to an internist for further evaluation and possible therapy.

Owners of dogs fitting the above criteria self-administered the CBPI on three occasions: at baseline, 1 week and 3 weeks later. Principal factor analysis with subsequent varimax rotation was used to ascertain whether the underlying factors identified statistically within data collected by the instrument were consistent with the theoretical factors associated with chronic pain that we were aiming to measure (severity of pain and impact of pain). The inter-item correlation matrix and item-total correlations were used to check for negative correlations and to screen for items with consistently weak correlations with other items in the scale.

The quadratic weighted kappa statistic was used to assess the first and second administrations of the instrument for test-retest reliability. Because pain scores are not normally distributed, nonparametric methods of analysis were used. Pain severity and pain interference scores were correlated with the global quality of life question using Spearman rank correlations. This was also used to assess the correlation between the severity and impact factors. The Wilcoxon signed-rank test was used to compare the severity and interference scores between the first and third administrations of the instrument. To determine whether changes in CBPI scores were associated with dog demographics, the

percent change in pain severity and pain interference scores were 1) correlated with the dog's age using Spearman rank correlations, 2) compared between dog breeds using the Krusal Wallis test, and 3) compared between dog genders, using the Mann-Whitney test.

For an extreme groups comparison, 50 owners of large breed dogs, greater than five years old (to represent the same signalment of dog that spontaneously develops bone cancer), were recruited from hospital faculty, staff and students via e-mail announcement. The dogs were considered clinically normal based on detailed history and physical examination. These owners self-administered the CBPI, and the Mann-Whitney test was used to compare severity and interference scores between dogs with bone cancer and clinically normal dogs. All analyses were performed in Stata version 8. A p-value ≤ 0.05 (2-tailed) was regarded as statistically significant.

Results

The owners of 100 dogs with a radiographic diagnosis of bone cancer completed the Canine Brief Pain Inventory (CBPI). Fifty-four percent of the dogs were male and 46% were female. The median age was 9 years (range 2 to 14 years). Twenty-six percent of the dogs were mixed breeds, 23% Rottweilers, 13% Labrador Retrievers, 6% Doberman Pinschers, and five percent or less of 16 other pure breeds were represented. The radiographic diagnosis of the bone cancer was primary bone tumor in 80% of the cases, soft-tissue tumor invading bone in 10%, and metastatic bone tumor in 10%.

The completion rate for all items was 99.8% and the instrument took less than five minutes to complete, confirming ease of use and minimal burden or ambiguity. The 10 items were entered into the orthogonal, varimax-rotated factor analysis. As hypothesized, two factors were identified with an eigenvalue greater than 1.0. The severity factor had an eigenvalue of 7.0 and the impact factor had an eigenvalue of 1.0 (Table 2). The remaining factors had eigenvalues ≤ 0.5 and retention of two factors was confirmed via scree plot. The two factors accounted for 81% of the variance. Cronbach's alpha was 0.95 and 0.93 for each of the factors, respectively, suggesting that the items in each of the two factors could be assessed as a group to compute factor scores (i.e., severity score and interference score). The average inter-item correlations were 0.83 and 0.69, respectively, with no negative inter-item correlations, demonstrating good internal consistency of the factors. Item-total correlations and communalities are shown in Table 2. The test-retest performance of the instrument was $\kappa=0.73$ and $\kappa=0.65$ for the severity and interference scores, respectively, demonstrating good stability of the instrument across repeated administrations.

For the convergent validity assessment, the scores correlated quite well ($r=0.49$ and 0.63, respectively) with the overall QOL question, such that as severity and interference scores increased, QOL decreased. In the comparison of extreme groups, normal dogs had significantly lower severity and interference scores than dogs with bone cancer ($p<0.001$) (Table 3). There was a significant increase in pain severity and interference score between the baseline and third week administrations of the instrument ($p<0.001$), suggesting that the instrument is able to respond to changes in the health status of the animal as the disease progresses (Table 3). There was no significant difference between males and females or among the various breeds in the change in severity and interference scores over time. In addition, there was no significant correlation between the age of the dog and the change in the severity ($r=0.18$) and interference scores ($r=0.19$). The severity and impact factors were moderately correlated ($r=0.68$), and demonstrated differences in correlation with the global QOL question indicating that they each tap into different aspects of the pain construct.

Discussion

We have established that the Canine BPI reliably measures owners' assessments of the severity and impact of chronic pain on their dogs with bone cancer. The severity and interference factors are moderately correlated consistent with their tapping into different but related aspects of the pain construct. The CBPI performed well in the various tests of validity. The two factors hypothesized a priori based on the BPI were consistent with those determined by factor analysis, with all items predictably loading preferentially into one or the other (i.e., construct validity). Dogs with bone cancer had significantly higher severity and interference scores than clinically normal dogs (i.e., extreme group validation). The severity and interference scores correlated moderately well with the QOL question, such that as scores increased, perceived QOL decreased (i.e., convergent validity). Further, the CBPI appears to be responsive to disease progression, in that the scores of both factors were significantly higher at the administration of the instrument three weeks following the first.

Evaluation of the performance of the scale in different types of cancers was not the focus of this study for several reasons. First, this was an observational study and most dogs had only a radiographic diagnosis because it is not standard of care to perform invasive diagnostics when an owner opts only for palliative care. Second, the pain is driven by the tumor's effect on the bone, such as osteolysis, nerve injury, and nociceptive mediator production in the bone-tumor microenvironment, rather than specific tumor histopathology.(31,32) Third, the purpose of the measure is to accurately record the pain experienced by the dog regardless of the underlying etiology. Like the BPI, the CBPI maintains internal consistency, stability, and positive validity assessments when applied to bone cancer pain from several potential etiologies.(23,33–38)

To better understand how the CBPI could be useful in improving preclinical efficacy evaluations of novel pain therapies, we should consider our findings in the context of animal use in human pain therapy development. Preclinical drug discovery has many steps, but often leads to mechanistic studies of the pain process in in vitro and in vivo rodent studies. Currently, these compounds are tested in experimental animal pain models, predominantly using tests to assess stimulus-induced pain (i.e., hot plate, tail flick, von Frey, etc.) before being considered for human studies. For bone cancer pain, a commonly used rodent model is to induce bone cancer via tumor cell injection into the long bones of rats or mice, after which disease progresses over two-four weeks from normal bone to severe osteolysis and pathologic fracture.(39–42) While these models mimic aspects of the human condition, there remains a substantial difference in the time course and progression of this disease and the outcome assessment is also dissimilar. As such, it has been difficult to predict how a change in latency on a hot plate test in rodent models will translate to outcomes in human clinical trials.(42–47) A spontaneous model with progression of a naturally occurring disease that measures chronic pain rather than experimentally induced models that measures acute stimulus-evoked pain may improve the predictability of preclinical studies to potential outcomes of human clinical trials.

With only 21% of drugs beginning phase I trials getting to market, and clinical period costs growing five times as fast as preclinical period costs(48), most large companies recognize that identifying better drug development models could be their best chance of modernizing the drug development process and preventing clinical trial failures late in development.(49) Companion animals spontaneously develop diseases that have clear parallels to human disease in pathogenesis, progression and symptomatology. Using these animals as models could be an effective intermediate step in screening for the efficacy of compounds that appear promising in induced rodent models, before committing them to human clinical trials. Having clear parallels in outcome assessment between animal studies and human

clinical trials is a logical component of a more predictive animal model. The fact that the CBPI and BPI reliably measure the same pain constructs in comparable spontaneous disease pathologies may allow the results of preclinical canine trials to better predict human clinical trial results.

The comprehensive assessment of pain in human clinical trials extends beyond pain severity to include how pain interferes with the patient's functioning through daily living. This is the same kind of assessment made by owners of dogs that develop bone cancer. The standard of care for dogs with primary appendicular bone cancer is amputation possibly followed by chemotherapy. However, many dogs do not receive this treatment, because their size and overall condition may prohibit amputation or, owners opt not to pursue aggressive procedures for their pet. For these dogs, the standard of care becomes managing the pain and loss of function caused by the bone tumor for as long as humanely possible, typically for several months after diagnosis. This evaluation of spontaneous pain and its impact on daily living as the pain process evolves parallels the human condition in a way that the rodent models do not. Recently, preliminary studies have shown that the companion canine model can be useful in evaluating the potential efficacy of novel antinociceptive agents.(50,51) Missing from these initial studies was the ability to quantify the outcome in a manner consistent with clinical outcomes important to dog owners and that parallel human disease.

The sound performance of the CBPI in validity and reliability testing may be in part attributable to using the same dimensional format, wording structure and response scaling as the well-validated BPI. There are two notable differences between the two scales. First, the BPI is most commonly used as a self-report instrument while the CBPI is an observer (owner)-completed assessment. However, observer (relative or caregiver)-completed assessments are commonly used in pediatric(52–60) and cognitively-impaired populations (61–64, 65{Chiu, 2005 #1296, 66). While the subjective worlds of young children, demented adults, and companion dogs are not directly accessible, readily interpretable behaviors observed over prolonged periods made by individuals knowledgeable about the study subject offer the basis for a valid assessment. Second, some behaviors commonly observed in the human experience of pain and included in the BPI were adapted to observed canine behaviors for the CBPI. The carefully selected elements reported as important by dog owners and their testing in an appropriate group of animals provides an understandable list of elements that map to a single factor in our analysis.

An additional concern in the development of any new scale is the acceptability to the intended population. The response of animal owners to our solicitation for volunteers was overwhelming, suggesting that animal owners did not object to participating in this research project. Besides potentially contributing to human pharmaceutical development, owners understand that pets may benefit directly from inclusion in the bridging veterinary trials and provide data useful for treating subsequent animals. By participating in funded studies, they also may have access to healthcare and interventions otherwise unavailable. Owners are grateful to have additional options for their pet, and many, particularly those whose dogs have terminal or life-threatening diseases, derive great comfort in knowing that the information gained from including their pet in a trial could benefit future generations of pets as well as people. Of the 200 dogs with bone cancer we have enrolled in trials of analgesic interventions, none have been lost to follow-up, a testament to owner dedication to the veterinary clinical trials process. The fact that study personnel become reliable resources to owners as they navigate difficult decisions for their pets through to the end of its life is an enrollment benefit that exists regardless of the efficacy of an intervention for any individual animal. The welfare of the animal is always the primary concern and systems for reviewing protocols that are outside the standard of veterinary care with an emphasis on evaluating risks and benefits to enrolled animals are routinely utilized in the approval process for

veterinary clinical trial. This parallels the review that occurs in human clinical trials and ensures that animals are properly protected from undue risk. Further, animals are only enrolled in trials following the written informed consent of their owner.

Conclusions

The development of new compounds to treat chronic pain has risen dramatically in the last decade. and there is a need for more predictive animal models to bridge the gap between discovery of a candidate compound and its introduction into humans(2,4,5). A novel approach to the development of animal models for assessing intervention efficacy is to focus on companion animals that spontaneously develop disease, and consider the outcome measures in that model that have meaning for animals as well as people. By focusing some efficacy studies on animals that spontaneously develop and naturally progress through the same diseases of clinical concern, with outcomes designed specifically to represent those of importance in human clinical studies, an animal model that yields efficacy results more predictive of clinical outcome could evolve. Further, the information gained in the testing of a novel therapeutic in these dogs is directly useful as preclinical data for human pharmaceutical development as well as clinical data for veterinary development, which could potentially benefit humans and animals.

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Table 1

Bridging the gap between experimentally induced rodent models of bone cancer and clinical bone cancer with the study of novel therapeutics in companion dogs with spontaneous bone cancer.

	Rodents	Companion Dogs	Patients
Disease	Induced	Spontaneous	Spontaneous
Progression	Rapid (days-weeks)	Intermediate (months)	Slow (months-years)
Evaluation Tools	Induced Pain via:	Spontaneous Pain via:	Spontaneous Pain via:
	hot plate	Canine Brief Pain Inventory:	Brief Pain Inventory:
	cold plate	severity	severity
	von Frey	interference	interference
	rotarod	quality of life	quality of life

Table 2

Factors, item loadings, item correlations and Cronbach's alpha for the Canine Brief Pain Inventory in dogs with bone cancer.

Factor and Items	Factor Loadings*	Communality+ h^2	Cronbach's Alpha#	Item-total Correlation**
Severity of Pain (Eigenvalue 7.09)			0.95	
Item 1: Pain at its worst	0.86	0.82		0.83
Item 2: Pain at its least	0.85	0.80		0.84
Item 3: Pain at its average	0.90	0.93		0.95
Item 4: Pain right now	0.86	0.86		0.90
Impact of Pain on (Eigenvalue 1.01)			0.93	
Item 5: general activity	0.68	0.84		0.88
Item 6: enjoyment of life	0.65	0.62		0.69
Item 7: ability to rise to standing	0.63	0.79		0.83
Item 8: ability to walk	0.72	0.82		0.85
Item 9: ability to run	0.89	0.87		0.81
Item 10: ability to climb stairs	0.85	0.78		0.71
Total Instrument			0.95	

*Factor Loadings are the correlations between the items and the factors. Loadings higher than 0.4 indicate that the item is highly correlated with the factor(67–70)

+Communality is the proportion of each item's variance that can be explained by the factor. If an item has a communality < .40, it may either not be related to the other items, or suggest an additional factor that needs to be explored.(67,71)

#Cronbach's alpha measures the extent to which the item responses correlate highly with each other. The alpha should be .70 or higher for a set of items to be considered a scale.(30,72,73)

**Item-total correlations are the correlations of the individual item with the total scale (with that item omitted). Items should correlate with the total score above 0.20 to be retained.(30,68)

Table 3

Canine Brief Pain Inventory pain severity and pain interference scores for 50 clinically normal dogs and 100 dogs with bone cancer.

	Normal Dogs		Dogs with Bone Cancer			
			Baseline		3 Weeks Later	
	Median	Range	Median	Range	Median	Range
Severity of Pain Score	0	(0, 0.75)	3.75	(0, 9.00)	4.25	(0, 9.00)
Pain Interference Score	0	(0, 0.67)	4.83	(0, 10.00)	5.26	(0, 10.00)