Characteristics and Impact of Animal Models Used for Sports Medicine Research

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abstract

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Animal models are commonly used for translational research despite evidence that the methodology of these studies is often inconsistent and substandard. This study describes the characteristics and impact of published research using animal models in the *American Journal of Sports Medicine* (AJSM).

Peer-reviewed articles published in the AJSM between January 1990 and January 2010 using animal models were identified using MEDLINE. The articles were reviewed for funding source, anesthesia used, animal used, study type, study location, outcome measures, number of animals, duration of animal survival, main topic being studied, and positive or negative treatment effect. The impact factor of the studies published between 2005 and 2010 was calculated. Two hundred fifty-seven articles, or 6% (257/4278) of the total publications during the 20-year period, were analyzed. The impact factor increased from 1.83 in 2005 to 3.9 in 2010. The most common animals used were rabbits (24%) and pigs (16%). The anterior cruciate ligament was studied in 34% of the articles, and a pig model was used for 31% of these studies. Eighty-six percent of the studies had a positive treatment effect.

This study shows that animal models used in sports medicine research lack uniformity in their methods and suggests that a publication bias may exist for animal research in the sports medicine literature.

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Animal experimentation is commonly used in an effort to advance medical knowledge.[1] Although it is a controversial subject on some levels, the Medical Research Council has shown that most people favor animal research if it can advance medical care for humans.[2] Animal studies are often performed for translational research, helping further evaluate unproven techniques or devices before they are used on humans. However, many clinicians may not be comfortable interpreting the results of, or conducting their own, animal research due to little understanding of what constitutes a valid animal research model.

Because animal studies are used for translational research, their results need to be carefully interpreted.[3] Although researchers can perform well-designed research projects using animals, such experiments should not be considered to have the same level of evidence as well-designed prospective clinical trials.[3] As with any type of research, innate limitations exist to animal models,[4] and it is important for researchers who are interested in using these models to understand these weaknesses so that faulty conclusions are not drawn from their work.[3]

Two common weaknesses seen in animal research are (1) models that lack consistency between studies and (2) models that do not accurately represent the clinical question they have been designed to address.[4-6] In addition, a publication bias[3,6] (articles that find significant results being more likely to achieve publication than a similar study that does not find a difference) and reporting bias[7,8] (the underreporting of undesirable or unanticipated results) may exist in animal studies. Considering that most animal research is used for translational purposes, these biases may lead to inappropriate conclusions being drawn that could negatively affect further studies.

With some countries providing more funding for animal research than human trials,[9] the inconsistencies between animal studies are notable. Although some of the discrepancies can be attributed to a lack of knowledge about the animal model being used, it is possible that resource and institutional limits further contribute to this problem. The goal of the current study was to evaluate animal studies printed in the *American Journal of Sports Medicine* (AJSM) to describe the characteristics, model types, and impact of published animal research in orthopedic sports medicine. These data may be helpful in establishing consistent animal models that can be used for common sports medicine questions and for minimizing the weaknesses and biases commonly associated with such studies.

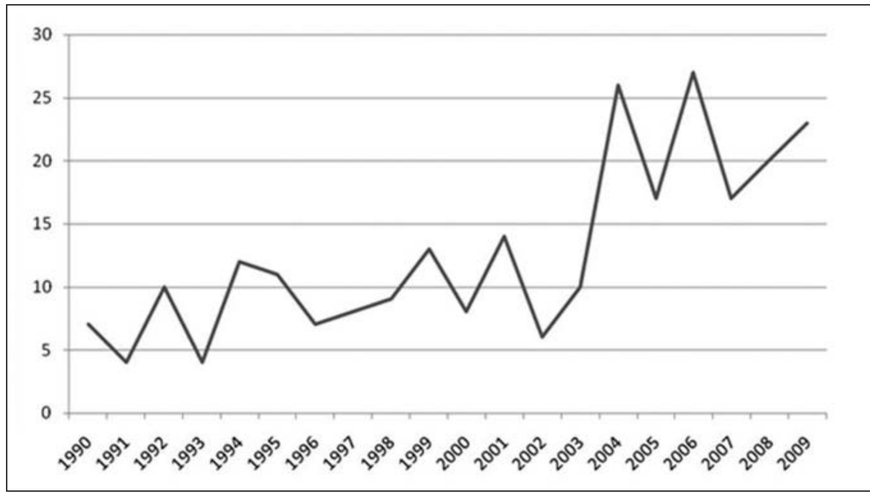

Figure: Number of publications per year in the *American Journal of Sports Medicine* that used animal models.

Materials and Methods

Peer-reviewed, original research articles published in the AJSM between January 1990 and January 2010 were reviewed with a MEDLINE search of the journal using the term *animal*. Manuscripts within the specified data range were screened for original scientific research using animal models. The included manuscripts were then reviewed with pertinent data recorded to characterize the animal models used for each publication and factors associated with publication.

The data recorded from the reviewed articles included outcome measure investigated (eg, biocompatibility, wound healing, implant investigation, or technique), outcome measurement tool used (eg, biomechanical, histological, or radiological [radiographs, magnetic resonance imaging, computed tomography]), study location (ie, United States or outside the United States), number of animals used, duration of animal survival, and primary funding source (eg, internal, industry, federal grant, nonprofit group, other, or unspecified). Positive or negative treatment effect was also recorded, with a positive study being one that supported its hypothesis or main purpose. Finally, sources the authors cited within the methods section of each article were recorded. Descriptive statistics were used to develop comparative analysis and identify trends.

In addition, an animal model–specific impact factor was calculated for the animal studies published in the AJSM between 2005 and 2010. To calculate this impact factor for each year, the number of times each paper was cited during the preceding 2-year period was divided by the total number of animal studies published during that same 2-year period. The number of citations during those time periods was determined by the Thomson Reuters Web of Knowledge Web site.

Results

Three hundred thirty-two articles were identified in the initial MEDLINE search. Of those 332 articles, 75 did not use an animal model and were excluded.

Two hundred fifty-seven published articles used animal models, which comprised 6% (257/4278) of all articles published in the AJSM during the period reviewed. Ninety-three of the animal studies were published between 1990 and 2000, accounting for 5.7% (93/1630) of all articles published during that time period. One hundred sixty-four of the animal studies were published between 2001 and 2010, accounting for 6.2% (164/2648) of all articles published during that time period. One hundred thirty of the animal studies were published between 2004 and 2010, accounting for 7.8% (130/1676) of all animal studies published during that time period (Figure).

Animal Model–specific Impact Factor

The animal model–specific impact factor for the animal models published in the AJSM increased from 1.8 in 2005 to 3.9 in 2010 (Table 1). This calculated impact factor was similar to that of the AJSM, and both had a similar increase over this time period.

Common Characteristics Among Published Studies in the AJSM

The majority (66%) of studies were performed at institutions within the United States, and it was most common for studies to not have a funding source identified (29%). The most common animal models were rabbit (24%), pig (16%), sheep (15%), and rat (13%). The most common number of animals used was between 10 and 19 animals (25%) and 40 and 49 animals (25%). Animals survived more than 30 days in 58% of studies and less than 24 hours in 2% (Table 2).

Table 1

Impact Factor of AJSM and Calculated Impact Factor of AJSM Animal Studies

	Impact Factor	
Year	AJSM	Animal Studies
2005	2.4	1.8
2006	2.7	2.4
2007	2.7	3.2
2008	3.4	3.4
2009	3.6	2.5
2010	3.8	3.9

Abbreviation: AJSM, American Journal of Sports Medicine.

Outcome Variables and Outcome Measurement Tools

The majority of studies were focused on biocompatibility (70%) and wound healing (60%). Of studies focused on the outcome of an implant, 36% were industry sponsored and 48% did not specify a funding source. Most studies measured their outcome variable using biomechanical (72%) or histological (60%) means. Some studies examined multiple variables and used multiple outcome measurement tools (Table 3).

Study Treatment Effect

Of the 257 studies examined, 220 (86%) had a positive treatment effect.

Common Subjects Studied

The most common subject matter evaluated was the anterior cruciate ligament (34%), followed by the meniscus (14%), cartilage (14%), and tendons (14%). Table 4 lists the most common animal models for each of the 5 most common subjects studied in the articles reviewed.

Discussion

The current study's results demonstrate that animal models are commonly used for research in articles published in

Table 2

Common Characteristics of AJSM Animal Studies

Characteristic	No. (%)
Study location[a]	
United States	170 (66)
Outside United States	98 (38)
Funding type[a]	
Internal	23 (9)
Industry sponsor	60 (23)
Federal grant	70 (27)
Not specified	75 (29)
Other	2 (1)
Nonprofit group	63 (25)
Animal type	
Rabbit	62 (24)
Pig	41 (16)
Sheep	38 (15)
Rat	34 (13)
Dog	30 (12)
Cow	20 (7)
Goat	18 (7)
Mice	4 (2)
Horse	4 (2)
Primate	3 (1)
Cat	2 (1)
Lamb	1 (0)
No. of animals	
1-4	13 (5)
5-9	25 (10)
10-19	65 (25)
20-29	49 (19)
30-49	64 (25)
50+	41 (16)
Animal survival	
Cadaveric	79 (31)
0-23 h	4 (2)
1-2 d	2 (1)
3-4 d	1 (1)
5-6 d	3 (1)
7-13 d	9 (3)
14-20 d	2 (1)
21-29 d	8 (3)
30+ d	149 (57)

Abbreviation: AJSM, American Journal of Sports Medicine.
[a]*Some studies were performed in multiple locations and had multiple funding sources, leading to percentages greater than 100% and total numbers greater than 257 in those categories.*

Table 3

Outcome Variables and Measurement Tools

Outcome	No. (%)
Variable studied[a]	
Biocompatibility	181 (70)
Wound healing	154 (60)
Implant	56 (22)
Technique	92 (36)
Measurement tool[a]	
Biomechanical	184 (72)
Histological	155 (60)
Radiological	29 (11)

[a]*Some studies had multiple variables studied and multiple measurement tools used, leading to percentages greater than 100% and total numbers greater than 257 in both categories.*

Table 4

Most Common Subjects Studied Using Animal Models[a]

Subject and Animals	No. (%)
ACL	88 (34)
Pig	27 (31)
Rabbit	17 (19)
Sheep	13 (15)
Cartilage	36 (14)
Sheep	9 (25)
Rabbit	7 (19)
Dog	6 (17)
Meniscus	36 (14)
Cow	8 (22)
Goat	6 (17)
Pig	6 (17)
Tendon	36 (14)
Rat	16 (44)
Rabbit	14 (39)
Dog	4 (11)
Rotator cuff	21 (8)
Cow	3 (14)
Sheep	3 (14)
Rat	2 (10)

Abbreviation: ACL, anterior cruciate ligament.
[a]*This table is not all-inclusive and only contains the most common variables found; therefore, percentages do not equal 100% in each category.*

the AJSM, with 257 such publications during the 20-year study period. More than half (52%) of the animal studies were published after 2004.

The influence of animal studies published in the AJSM appears to be increasing because the animal model–specific impact factor increased from 1.8 in 2005 to 3.9 in 2010. The animal model–specific impact factor was similar to that of the AJSM in number and in upward trend over the past 5 years. These data suggest that clinical journals may be able to expose their readership to emerging therapies that are still at the preclinical status while not hindering their impact factors.

A wide variety of animals were used in these studies, with some animals preferred for specific subjects. Pigs were the most common animal used for studies involving the anterior cruciate ligament (ACL) (31%). Meanwhile, rats and rabbits were the most common animals used in studies evaluating tendons and muscles. These trends make intuitive sense. Larger animals have larger joints and intra-articular ligaments, making their use for the evaluation of synovial joints like the knee easier, whereas rats and rabbits are less expensive and have tendons and muscle bellies that are easy to expose and harvest. In addition, certain animals have specific joints or bone and muscle structures that closely resemble those of humans.[10] Using these previously described comparisons may ease setting up the experiment and explaining how the animal studies may be used in a translational capacity. Of note, a frequently referenced orthopedic-focused animal research text does not list pigs as a commonly used animal for ligament research, despite their having been the most frequently used animal for ACL research in the current study.[11]

Specified funding was nearly equal between federal, private, and industry sources when reported. The amount of industry funding found was not surprising because many of the new sports medicine techniques and advances in technology involve implants and devices made by companies within the orthopedic industry. In these instances, industry is often eager to show the usefulness of their product and, therefore, is willing to fund animal-based research that may show the benefits of their product. When looking specifically at the studies of orthopedic implants, 36% were primarily funded by industry. The true percentage may be even higher considering that 48% of the studies evaluating orthopedic implants did not specify where the funding for their study came from.

Funding is crucial for animal studies because a significant cost is often associated with their completion. At the authors' institution, the cost of a 30-day experiment using 40 small animals, such as rats, with 1 surgical procedure would be more than $15,000 for the entire group. For 40 large animals, such as pigs or sheep, the cost is approximately $50,000. These costs are on the conservative side because they include only 1 surgical procedure and do not take into consideration associated costs of the study (ie, computed tomography scans or biomechanical testing) or the personnel required to complete these studies, which typically costs more than the animals. Lack of funding may be a reason that many of the animal studies examined were completed on cadaveric animals (31%).

Only 14% of the studies examined in the current study had negative results. This suggests that a publication bias may exist in sports medicine animal research. Such a bias would mean that studies that showed a difference between groups would be published more often than studies using the same methodology that did not show a difference between groups. This is similar to other findings suggestive of publication biases in the surgical literature.[12,13] It is possible that this bias exists because researchers who conduct studies that do not show significant differences between groups feel that such results do not contribute to the medical literature and, therefore, do not make an attempt to publish the data. This is commonly referred to as the "file drawer effect," in which studies that do not produce significant results are stashed away in a drawer without being published.[13] However, if animal studies are not submitted for publication or are not published because of negative results, conclusions formed based on the potentially biased data that has been published may lead to inaccurate conclusions. With animal models being used in a translational role for many new treatments, such a publication bias could possibly lead to human trials being sought and conducted based on a faulty premise.

A limitation of the current study is that the methodology and statistical analysis of each study were not critically examined. Such information would provide insight into the quality of the animal studies being published. This knowledge may have revealed weaknesses within subgroups of animal research and helped future investigators address these weaknesses and develop improved animal research models.

Using the data obtained in this study, the authors compiled a list of animal models for sports medicine research (Table 5). These models are based on the most common practices for the successfully published articles in each subject. In addition, a rough estimate of the cost to complete the entire experiment at the authors' institution using the suggested models is listed. The most commonly cited methodology references for each subject are listed (Table 5). However, most listed sources are not animal models, and no source was referenced more than 5 times in 257 articles. This lack of citations strongly suggests that few, if any, gold standard animal models exist for investigators to follow and makes it difficult to compare results across studies.

Table 5

Projected Animal Models, Their Cost, and the Most Commonly Cited References for Common Sports Medicine Research Topics

Subject	Type of Animal (Species Commonly Used)	No. of Animals	Length of Survival	Estimated Cost, $[a]	Most Common References
Meniscus	Large (dog, cow, goat)	30	7 d	67,000	1, 11, 14
ACL	Large (pig, sheep)	20	30 d	49,000	13, 16, 29
Cartilage	Large (sheep, dog)	30	90 d	92,000	17, 19, 20
Rotator cuff	Large (cow, sheep)	20	30 d	49,000	14, 15
Tendon	Small (rat)	40	<24 h	12,500	6, 7
Muscle	Small (rat)	40	<24 h	12,500	3, 5, 28

Abbreviation: ACL, anterior cruciate ligament.
[a]*Costs are based on estimates to complete the entire research project at the authors' institution.*

Conclusion

It is important for models to be replicated in the published literature to allow for direct comparison between studies and minimize confounders in the sports medicine literature. As seen by the increasing number of publications and improvement in the animal model–specific impact factor score in recent years, animal models continue to play an important role in sports medicine research. Without common models, clinician scientists will struggle to validate their results and build off of previous studies. While this study describes the characteristics of successfully published animal studies in the hopes of minimizing the variance between such studies, it also highlights the need for standardized study models. Doing so will help optimize how animal models are used to further the field of sports medicine.

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