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.
### Characteristics and Impact of Animal Models Used for Sports Medicine Research

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A
mial experimentation is com-
monly used in an effort to ad-
vance 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, help-
ing further evaluate unproven techniques
or devices before they are used on hu-
mans. However, many clinicians may not
be comfortable interpreting the results of,
or conducting their own, animal research
due to little understanding of what consti-
tutes 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 limita-
tions exist to animal models,4 and it is im-
portant 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) mod-
els that do not accurately represent the
clinical question they have been designed
to address.5,6 In addition, a publication
bias3,6 (articles that find significant results
being more likely to achieve publication
than a similar study that does not find a
difference) and reporting bias5,6 (the un-
derreporting of undesirable or unantici-
pated results) may exist in animal studies.
Considering that most animal research
is used for translational purposes, these
biases may lead to inappropriate conclu-
sions being drawn that could negatively
affect further studies.

With some countries providing more
funding for animal research than human
trials,5 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 in-
titutional 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 ani-
mal research in orthopedic sports medi-
cine. These data may be helpful in es-
tablishing consistent animal models that
can be used for common sports medicine
questions and for minimizing the weak-
nesses and biases commonly associated
with such studies.

MATERIALS AND METHODS

Peer-reviewed, original research ar-
ticles 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 scient-
ic research using animal models. The
included manuscripts were then reviewed
with pertinent data recorded to charac-
terize the animal models used for each
publication and factors associated with
publication.

The data recorded from the reviewed
articles included outcome measure in-
vestigated (eg, biocompatibility, wound
healing, implant investigation, or tech-
tique), outcome measurement tool used
(eg, biomechanical, histological, or ra-
diological [radiographs, magnetic reso-
nance imaging, computed tomography]),
study location (ie, United States or out-
side the United States), number of ani-
mals used, duration of animal survival,
and primary funding source (eg, internal,
industry, federal grant, nonprofit group,
other, or unspecified). Positive or nega-
tive treatment effect was also recorded,
with a positive study being one that sup-
ported 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 iden-
tify trends.

In addition, an animal model–spe-
cific 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 pre-
ceding 2-year period was divided by the
total number of animal studies published
during that same 2-year period. The num-
ber of citations during those time periods

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

Outcome Variables and Outcome Measurement Tools

The majority of studies were focused on biocompatibility (70%) and wound healing (60%). Of those 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 1

<table>
<thead>
<tr>
<th>Year</th>
<th>AJSM</th>
<th>Animal Studies</th>
</tr>
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<tbody>
<tr>
<td>2005</td>
<td>2.4</td>
<td>1.8</td>
</tr>
<tr>
<td>2006</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>2007</td>
<td>2.7</td>
<td>3.2</td>
</tr>
<tr>
<td>2008</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>2009</td>
<td>3.6</td>
<td>2.5</td>
</tr>
<tr>
<td>2010</td>
<td>3.8</td>
<td>3.9</td>
</tr>
</tbody>
</table>


Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study location</td>
<td>170 (66)</td>
</tr>
<tr>
<td>United States</td>
<td>98 (38)</td>
</tr>
<tr>
<td>Outside United States</td>
<td>72 (27)</td>
</tr>
<tr>
<td>Funding type</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Internal</td>
<td>60 (23)</td>
</tr>
<tr>
<td>Industry sponsor</td>
<td>70 (27)</td>
</tr>
<tr>
<td>Federal grant</td>
<td>75 (29)</td>
</tr>
<tr>
<td>Not specified</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>63 (25)</td>
</tr>
<tr>
<td>Nonprofit group</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>


Table 3

<table>
<thead>
<tr>
<th>No. of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
</tr>
<tr>
<td>5-9</td>
</tr>
<tr>
<td>10-19</td>
</tr>
<tr>
<td>20-29</td>
</tr>
<tr>
<td>30-49</td>
</tr>
<tr>
<td>50+</td>
</tr>
</tbody>
</table>


*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.
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 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.\textsuperscript{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.\textsuperscript{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.

**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.

**REFERENCES**


