

Review Paper: The necessity of continuous analysis of animal model utilization in the experimental medical researches



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ABSTRACT

Over the years and especially in recent decades, numerous articles in the field of *in-vivo* studies have been published; hence, the major part of medical discoveries that has led to increased life expectancy is as a result of these studies. The importance and inevitability of *in-vivo* studies have proven and no real alternative to animal models has been introduced so far. In this regard, the extent of authors' familiarity with *in-vivo* researches and the existence of biomedicalists for various measurements in animal models are highly important. Furthermore, resemble of animal models to human multifactorial diseases and the plenty of evidence for invasive interventions as well as the role of stress and genetic similarity should be considered in *in-vivo* studies. Therefore, due to waste of time and financial resources as well as animal rights and welfare, the existing animal models and methods should be constantly criticized. This article attempts to address this important issue of comparative biomedicalists.

1. Introduction

Use of animals in the experimental medical researches is common, and the progresses, such as invention of vaccines, without using the animal models, would not be possible [1]. Consequently, over the years, and especially in recent decades, numerous articles in the field of *in-vivo* studies have been published. Nevertheless, analysis of the applied methods, moral standards, and

the similarity between animal models and humans were not comprehensively evaluated. This article attempts to emphasize on the importance of continuous analysis of comparative and experimental medical studies, and the need for "reasonable doubt" in the accuracy of *in-vivo* investigations, using several examples.

2. The need for criticism in medical *in-vivo* studies

1. Animal dignity and rights require that articles

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be morally criticized [2]. The basic questions in this regard are:

- A. In principle, is there a way to confirm the authors' claim, stating that they have observed the ethical standards?
 - B. Do all the researchers have the understanding of ethical issues?
 - C. Is the issue of ethics unaffected by the culture of different nations?
 - D. Is it possible to monitor ethical issues without independent committees, including experts?
 - E. Whether or not one can assess the 3R through reading an article?
 - F. To what extent are authors familiar with animal models in order to ensure animal welfare?
- Hence, it seems logical to have an ethical correspondence along with scientific correspondence in every article.

2. Each measurement in medical *in-vivo* studies requires an expert, otherwise the findings cannot and should not be considered as reliable. For example, interpretation of histopathologic slides should be performed by an animal pathologist; hence, due to importance of medical *in-vivo* studies, the presence of veterinary/comparative pathologist is a necessity [3], and the question is, has this issue been considered in articles?

3. Invasive interventions are associated with severe pain and destruction, e.g. experimental skin burn, can only be done if there is "plenty of evidence". This means that there should be evidence of success of *in-vivo* findings in the clinical trial, and then improves patient's condition. Due to availability of rodents as well as their low cost, a great deal of research is conducted on these type of animals, but at least for 3 reasons, this group of studies should be scrutinized:

- A. The small size and rapid recovery of experimental burns in rodents does not resemble human burns.
- B. Hot metal rod induced burn is always affected by the operator hand pressure. As a result, the depth of burn is usually different; thus, producing inconclusive and unrepeatable results.
- C. In several papers, authors claimed that they induced third degree burn in an animal; however, this grading system is only applicable in human clinical medicine; consequently, inaccurate, subjective and absolutely inappropriate for the evaluation of experimental burns. Creating burn at the same depth is a function completely depen-

dent on temperature, time as well as the operator hand pressure [4, 5]. The degree of experimental burn should be determined histologically, but not clinically. A word of caution, the temperature of a hot metal is very high and can result in very deep and uncontrolled burn, which in turn is not moral. Based on what was mentioned, the results of many researches on experimental burns are likely to be deviated [6].

4. In the case of multifactorial, infectious, auto-immune and mental illnesses, the problem is more complex. A good example is ulcerative colitis (U.C). In the literature, different causes such as genetic, environmental factors and immunological disorders have been mentioned [7]. The simplest and cheapest method to induce the disease is through the creation of ulcer at the end of rat colon by acetic acid [6, 8], but, does this really resemble human U.C? The issues should be considered in this regard are:

- A. The disease is quite chronic in humans while it is quite acute in the animal model.
- B. Unlike human disease, this kind of experimental wounds in the animal model will heal quickly, even if left untreated.
- C. Unlike human disease, an experimental U.C in an animal model is chemically induced, and as a result the psychological effects of the diseases are ignored.
- D. Some of the available therapies in animal models are based on enema with no clinical benefit.

Subsequently, how can the results of such experiments be of any use in medicine?!

5. Generally, in the experimental research, one of the variables is considered and the others are excluded, which makes it true that the existence of different variables makes it impossible to conclude and interpret the results. Therefore, in *in-vivo* studies, species, breed, age, sex, weight, nutrition and animal husbandry conditions are quite uniform, but can the results of such research be extended to a highly diverse human society? Of course, repeating the experiment on different species, breeds, age group and genders can help to validate the findings, but then again due to high cost, this is impossible.

6. It is also farfetched to eliminate stress due to handling, restriction and sampling of animals, which can certainly have an impact on the findings [9].

Table 1: Summary of concerns regarding the utilization of animal models in the experimental medical researches

Number	Major concerns
1	Animal dignity and rights, ethical standards and moral criticism
2	Expert researchers
3	Invasive interventions without plenty of evidence
4	Problems regard to multifactorial, autoimmune and mental illnesses
5	Generalization of an <i>in-vivo</i> research to highly diverse human societies
6	Role of stress and environmental factors
7	Role of sacrificing methods
8	Single-organ studies
9	Generalization of extracts to real human diet
10	Staying a neutral researcher
11	Best animal model for each type of experimental research
12	Sensitivity of animal models
13	Dose selection methods
14	The genetic similarity between animal models and human

7. How the animals are sacrificed, has a direct effect on their tissues. For example, drug or gas usage has a direct effect on the rate of post mortem changes. Disregarding the very important issue of post-mortem changes will result in autolysis in some microscopic images [10].

8. Single-organ studies in the experimental toxicological pathology might have little effect on promoting human health. In other words, if the effect of one substance on all organs is not examined, it won't have a significant impact on the development of medical science.

9. Sometimes, the use of medicinal plants in animal models does not have a practical usage in humans. For example, a plant eaten by humans at a reasonable interval combined with other foods cannot be inoculated as an extract into the animal diet. Generally, animals are exposed to high concentration of a substrate in a short period; thus the results cannot be reliable, and it seems that the only real option is to feed the animals, using real human diet in the same fashion and time period [11].

10. Staying neutral as a researcher is very difficult. For example, it is not easy to express the inadequacy of traditional medicine or ancient medicinal plants by animal models. In this case, the animal model is used as a scientific tool to prove the old belief.

11. Choosing the best animal model has always

been a challenge. For example, the vertical position of the birds and the distribution of body weight over 2 feet made these animals a suitable model for human foot and skeletal disease [12]. However, this animal model is not well understood by experimental medical researchers in the field of orthopedic diseases.

12. Highly sensitive models such as chick embryos should be used very carefully. Although these models are inexpensive and available, they exhibit dramatic changes due to their high sensitivity in reaction to a very small dose of a substance [13]. Using such models requires experience and practice; otherwise, it will have misleading results.

13. Laboratory animals are widely used in toxicological studies in order to evaluate the toxic mechanism of consuming compounds in human and animals. Dose selection is a complex procedure in experimental studies. Extrapolation of initial dose between laboratory animals, humans or other animal species is the most important step in comparative biomedical investigations. Body weight, body surface area and interspecies biochemical and physiological differences should be considered carefully. Furthermore, there must be sufficient reason to use overdose. It is clear, however, that increasing the dose is always accompanied by changes in the tissues. But this finding does not prove anything in itself [14-18].

14. The genetic similarity between humans and the animal model chosen in a particular subject is the most important issue [19]. However, many articles do not address this issue at all. A number of concerns regarding the utilization of animal models in experimental medical researches are presented in Table 1.

3. Conclusion

Historically, the importance and inevitability of *in-vivo* studies have proven. Contrary to the opinion of some authors, no real alternative to animal models has been introduced so far. But since the findings of such researches are based on the suffering and killing of animals, they must be continually criticized. Otherwise, the number of articles will increase every day without contributing to the health of the human community. Thus, the possible mission for comparative medicine professionals is to analyze and improve existing methods and introduce new models and methods. But this is impossible except with doubt in paradigms.

Ethical Considerations

Conflict of interest

No conflict of interest to declare

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