

## Preclinical Oral Histology Research: A Retrospective Review Study

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### Abstract

A retrospective study is conducted to identify factors that improve prospective animal studies; contribute to the optimization of animal protection from all unnecessary and preventable damage. Preclinical oral histology research from 2010–2020 is evaluated and 64 studies were reviewed relating to two interventions: bone trauma and surgical incision. The harm-benefit analysis is featured in this study through the application of the recent form of Bateson's Cube. Depending on its three axes, we can assess animal suffering, the likelihood of benefit, and the importance of research. The total number of animals used in the research is 2685. Rats, 51.6%, and rabbits, 48.4%, are the most commonly used animals. Research related to bone healing accounts for about 65.6%, while research related to wound healing 34.4%. The expert panel's estimate of animal suffering revealed that 57.8% had moderate animal suffering; 39.1% had mild suffering, and only 3.1% had severe suffering. Results revealed that hard tissue studies get more citations, 77.88% more than soft tissue-related research. However, the soft tissue studies show more concordance between preclinical and clinical studies. Continual efforts should be made to assure that when animals are involved in research, each study is well-designed, well-analyzed, and clearly published.

### Introduction

Histology is the science and study of normal tissues. Oral histology in vivo research focuses on the development and structure of cells and tissues. Most studies focus on hard tissue, as an example, bone healing and soft tissue wound healing. [1,2].

It is well known that the primary objective of animals in research is to get accurate and highly efficient scientific information, and that knowledge cannot be achieved without the use of laboratory animals. Moreover, when using experimental animals, the researcher must follow the Three Rs (3Rs) guiding principles for more ethical use of animals in product testing and scientific research; replace them with other alternatives (Replacement), to use the least number of them (Reduction), and utilize those animals optimally (Refinement) [3,4].

Every year, 50–100 million vertebrates are used in experimental in vivo studies around the world. The use of animals for research is legally regulated with the explicit understanding

that such use will provide significant new knowledge, facilitating relevant benefits, and that no unnecessary harm will be imposed on the animals [5,6].

Without a doubt, researchers must create a clear research protocol that explains the study methodologies and processes used while adhering to the following criteria: The necessity to protect these living creatures from pain, disruption, and fear when they remember these experiments, considering scientific planning and precaution for any animal study should be based on a scientific informational research technique approved by the university's Ethics Committee for Scientific Research and the Use of Experimental Animals [7,8].

Furthermore, consult a veterinary physician to know the conditions and status of the laboratory animals before, during, and after conducting experiments in order to preserve the general health of those working on them and to guarantee that infection does not spread among animals or those who deal with them [9,10].

Additionally, if possible, use alternatives to animals in conducting research, such as cell and tissue cultures or electronic simulation tests. Certainly not to perform experiments on endangered species unless for the purpose of increasing their reproductive rates, and only with legal approval (from the appropriate authorities) and in conformity with the legislation in place to protect environmental life [11,12,13].

It is absolutely better not to re-use previously used experimental animals. The use of euthanasia for animals following the completion of experiments or the loss of certain essential organs in order to stop the animal's suffering as a result of the intense pain caused by such tests [14,15,16]

Animal models allow researchers to naturally produce or genetically design a skeletal phenotype linked to diseases, as well as conduct destructive fracture tests on bone to assess the consequent change in mechanical characteristics [17,18].

Rodents are constantly being used in biomedical research. Laboratory rats and mice are good animal models for comparative medicine studies because they have so many anatomical and physiological similarities to humans. Rodent models are considered important in preclinical bone research. They give information on bone metabolism and highlight positive or negative impacts from the use of specific medication [19].

Histological studies of rats' calcified tissues are conducted in clinical and research laboratories all over the world, and they are critical for understanding anatomical morphological and pathophysiology. Furthermore, they also enable us to research the normal process of bone repair. Rat bone healing models are extremely useful because of their surgical accessibility and standardization [20,21].

Rodent femurs and tibiae, in particular, are suitable for experimental research, and each has its own set of advantages and limitations. A large muscular layer surrounds the femur, making the creation of a normal fracture more difficult. As a result of the soft tissue coverage, implants can be used with minimal complications and infection rates. Furthermore, by far the greatest number of fracture models have been built on the femur, allowing for comparisons between studies. On the other hand, the tibia's thin, soft tissue coverage makes it easy to

access and use this bone for closed fracture models with or without intramedullary stabilization devices [19,22].

Despite the structural differences between rat and human skin, countless studies have been conducted on these species. Rats are an ideal model for skin wound healing because they allow for conformity of the size, shape, and thickness of the wound injury [23,24].

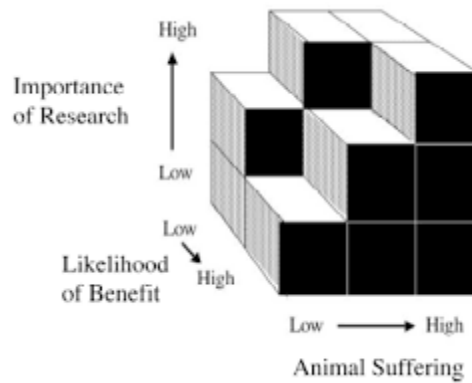
Additionally, the second most commonly used animal is the rabbit, which is a widely used experimental model for oral surgery and implantology tests. It has a convenient size, is inexpensive, and it has a physiology comparable to humans. One of the rabbit's main advantages is that it reaches its skeletal maturity shortly after reaching its sexual maturity, which is at 6 months [25,26].

For many years, rabbits have been used as a wound healing model known as the rabbit ear excisional wound model. Wounds caused by a biopsy punch include epidermis, dermis, and cartilage injury. In contrast to murine models, the healing happens from the edge inwards and there is no contraction. One of the rabbit skin wound advantages is that it heals by re-epithelialization [27].

Overall, experimental animal wound models have advantages. They allow for the investigation of multiple elements of the healing process, as well as the selective depletion of specific genes to determine their effect on wound healing; the study of a functional immune system; the creation of multiple wounds within a single animal; and the modeling of various wound healing sources [28,29].

Experimental animal wound models, on the other hand, have limitations, such as the complexity of the entire animal, which prevents a clear assessment of the contributions of tissues or cells throughout the healing process. The immune response may differ from that of humans; the size, depth, and dimensions of the wound may be difficult to manage; and no precise and repeatable chronic wound model representation has been established [27,30].

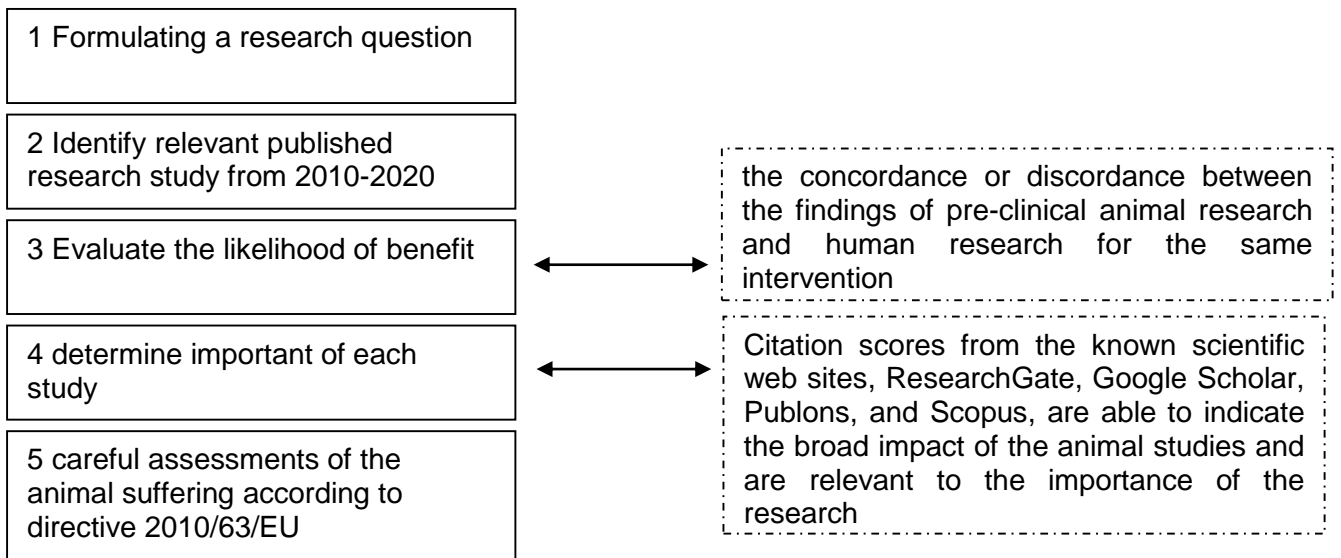
We all agree that what laboratory animals provide to humanity is something worth respecting and appreciating. Preclinical experiments on animals have been confirmed to be essential, but we should take into consideration that the use of animals must be justified. Harm-benefit analysis (HBA) is regarded as an important ethical safeguard for laboratory animals used in preclinical research. For each in vivo study, we should predict and measure the harms that cause suffering to experimental animals, as well as weigh those harms against the research's expected benefits. Those benefits must be considered significant enough to outweigh the harms [31]. Professor Patrick Bateson developed the cube as a model of harm-benefit analysis figure 1. The decision cube, with its three axis; animal suffering, the likelihood of benefit, and the importance of research, is a convenient way to weight up ethical decisions [32,33].



**Fig.1** Bateson cube as a model of harm-benefit analysis

**Method:**

The study, conducted at Baghdad University College of Dentistry, targets mainly online published research from 2010\_2020. It took numerous measures to achieve its purpose, which is summarised briefly in Diagram 1. Thereupon, we applied the most recent version of Bateson's Cube to evaluate HBA; for the animal suffering axis, the panel severity classification is used, and each research intervention was categorized as mild, moderate, or severe box 1 [20]. The likelihood of benefit is determined by the concordance or discordance between the findings of pre-clinical animal research and human research for the same therapies, with concordance indicating that animal studies are properly used as a model for human clinical trial [34]. Citation scores are able to indicate the broad impact of the animal studies and are relevant to the importance of the research axis.



**Diagram 1:** Retrospective Review Steps to evaluate HBA

If the research causes mild animal suffering, assured to be beneficial and with high citation scores, then it will fall into the hollow section of the cube, meaning research should proceed. Painful, low-quality research with a low benefit will be positioned in the solid part of the cube and, with no doubt, should not be allowed to be considered.

### **Mild**

Procedures on animals as a result of which the animals are likely to experience short-term mild pain, suffering or distress, as well as procedures with no significant impairment of the well-being or general condition of the animals.

### **Moderate**

Procedures on animals as a result of which the animals are likely to experience short-term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress, as well as procedures that are likely to cause moderate impairment of the well-being or general condition of the animals.

### **Severe**

Procedures on animals as a result of which the animals are likely to experience severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress, as well as procedures that are likely to cause severe impairment of the well-being or general condition of the animals.

### **Non-recovery**

Procedures which are performed entirely under general anaesthesia from which the animal shall not recover consciousness.

**Box 1.** Severity categorised according to directive 2010/63/EU [20]

## **Result**

Sixty-four papers from 2010–2020 were reviewed; the total number of experimental animals involved in the studies is 2685, including rats (51.6 %) and rabbits (48.4%). Table 1 summary of the published studies reviewed in the research.

**Table 1:** publication dates, study type and numbers of animals

Publication date of studies	No. of studies	Type of study	Type of experimental animal	No. of experimental animal
2010	4	3 related to bone healing 1 related to skin healing	Rats and rabbits	84
2011	8	Bone healing	Rats and rabbits	408
2012	5	4 bone healing 1 skin healing	Rats and rabbits	222
2013	8	6 bone healing 2 soft tissues	Rats and rabbits	445
2014	10	7 bone healing 3 soft tissues	Rats and rabbits	444
2015	4	2 bone healing 2 soft tissues	Rats and rabbits	175
2016	2	1 bone healing	Rats and rabbits	120

2017	9	1 soft tissue 5 bone healing 4 soft tissues	Rats and rabbits	321
2018	5	1 bone healing 4 soft tissues	Rats and rabbits	172
2019	4	2 bone healing 2 soft tissues	Rats and rabbits	142
2020	5	3 bone healing 2 soft tissues	Rats only	152

More than half of the studies, 57.8%, have moderate animal suffering; 39.1% have mild animal suffering; and only 3.1% have severe animal suffering, according to the panel severity classification.

Preclinical experimental research on two interventions that are the focus of this review study reveals that 65.6% relates to bone healing after intentional bone trauma and is conducted to study how to facilitate bone healing by applying some plant extract either with or without the use of an implant, and 34.4% relates to soft tissue healing after a premeditated surgical incision.

The animal studies were first published before human studies. Soft tissue research is used as a model for human clinical trials 22.7% of the time, while 16.7 % from the hard tissue research use as references in clinical studies. Table 2. Publication dates of animal studies and human studies

**Table 2:** Comparison of dates of animal and human studies.

Type of the study	Publication dates of animal studies	Publication dates of human studies
Bone healing studies	2010	2014 2015 2019 2020
	2011	2013 2016 2018 2019 2020 2022
	2013	2018
	2014	2020
Soft tissues healing	2014	2016 2020

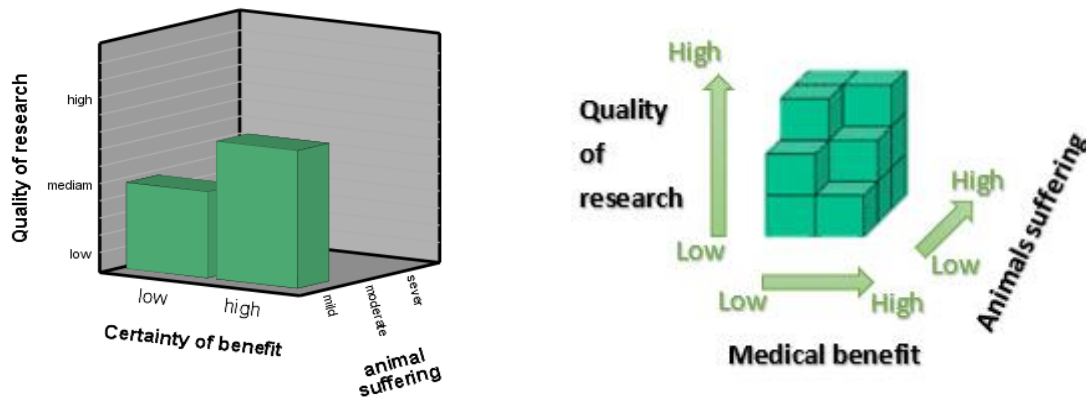
	2015	2019 2020
	2019	2020

The citation scores as an indicator of the importance of the research were manually counted from the known scientific web sites, ResearchGate, Google Scholar, Publons, and Scopus. The results revealed that bone-related experiments get more citations, 77.88% more than soft tissue-related research, 22.15% Table 3.

**Table 3:** Citation scores.

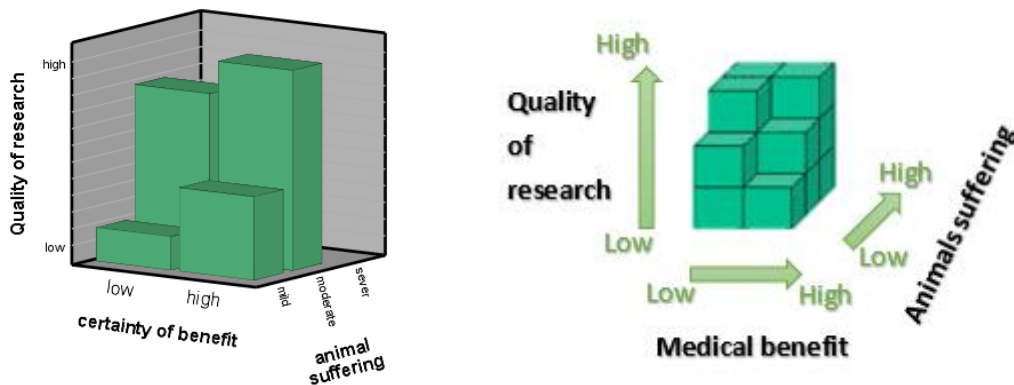
Intervention	No. studies	Total No. citation	Average citation
Bone healing	42	137	3.26
Wound healing	22	39	1.77

Applying Bateson's cube for hard tissue-related research Figure 2, the quality of research is medium to high so it takes the top layer, certainty of benefit high meaning it would be on the right side, finally, since the animal suffering is medium, it's meet in a hollow cube so we can be processed with the researches.



**Fig. 2** Bateson's cube for hard tissue-related research

When applying Bateson's cube for soft tissue-related research Figure 3, the quality of research is medium so it takes the median layer, certainty of benefit high meaning it would be on the right side, finally, since the animal suffering is mild, it's meet in a hollow cube so we can be processed with the researches.



**Fig. 3** Bateson's cube for soft tissue-related research

## Discussion

Retrospective studies are the fundamental basis for all prospective research. Certainly, if we make it obligatory to revise previous articles every few years, we can make sure that the three R's principles by Russell and Burch are applied in a way that certain lives of each experiment animal are precious and used for noble goals. Several models for harm-benefit analysis have been discovered, and the Bateson cube is a visual model that illustrates the concept of harm-benefit analysis in a practical way [35,36].

The levels of severity used to classify harm caused by experiments on animals are mild, moderate, severe, and non-recovery. The majority of oral histology studies are mild to moderate. Most soft tissue-related studies focus on wound healing, which causes animals to experience short-term minor pain, suffering, or distress, and such experiments have no substantial impact on the animals' general health. On the other hand, studies of hard tissue when bone healing is the subject of studies, in most cases, are associated with implants, and as a result, there is a moderate level of harm and animals experience short-term moderate pain, suffering, or discomfort and, moreover, long-term mild pain, suffering, or distress. Consequently, animals are expected to have a moderate effect on their general health.

Furthermore, the results revealed that hard tissue-related studies get more citations, which gives such research a high quality. This can be explained by the fact that this research uses bone models to study dental implant improvement materials and/or methods. This agrees with the findings of Jayachandran et al. 2021, the quality of dental implant researches has improved in the past two decades [37].

However, the studies focusing on skin or oral mucosa healing after surgical incisional wounds are more beneficial and, as the results showed, are used as a model for human clinical trials at a high rate. Undoubtedly, such research focuses primarily on the role of plant extracts in facilitating wound healing are getting more attention. Nowadays integrating traditional knowledge of medicinal plants with modern research efforts gives a new technique that significantly improves the rate of drug discovery. Herbal remedies are gaining popularity when nature-derived products are used to improve human health and, in particular, to enhance wound healing. As this finding is supported by the review study of Dorai 2012, traditional medicine extracts derived from plants and flowers are used to heal wounds at high

rates. Due to the rising expense of health care, particularly wound care, it is more cost-effective to treat wounds with traditional medicine [38].

As shown above, scientists must realize their responsibility to conduct preclinical experimental research and seek expert opinion on aspects impacting the condition of their study animals, while also considering the influence on science as well as animal welfare. Wherever possible, the HBA should be based on the most recent scientific data on harm. Where these datasets are not available, efforts should be made to get them through cross-organizational exchange [31,39,40].

In summary, researchers and the ethical community should apply retrospective harm-benefit analyses to future proposals that use the same or comparable methodologies. The information obtained from these assessments should provide opportunities for institutions to identify areas for improvement in order to make each research conducted with maximum benefit and minimal harm to the creatures that provide humanity with a plethora of facilities to discover the causes, diagnose, and treat disease in humans and animals.

## **Conclusions**

We recommend that retrospective review be used in close collaboration with prospective studies. Continual efforts should be made to assure that when animals are involved in research, each study is well-designed, well-analyzed, and clearly published. Any sort of harm inflicted on an animal should be handled professionally and minimized to the greatest extent possible. One main goal of this review is to assist and encourage those who use and conduct experiments on animals to do things differently and better, with the goal of maximizing the benefit over the harm.

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## **Conflict of interest statement**

The authors declare no conflicts of interest.

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## بحوث أنسجة الفم قبل السريرية: مقال استعراض مراجع

مریم حمید علوان

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### الخلاصة:

أجريت دراسة بأثر رجعي لتحديد العوامل التي تحسن الدراسات الحيوانية لتحقيق أكبر فائدة بأقل ضرر للحيوانات المختبرية؛ المساهمة في تحسين حماية الحيوانات من جميع الأضرار غير الضرورية التي يمكن الوقاية منها. تم تقييم الأبحاث ما قبل السريرية المتعلقة بأنسجة الفم من عام 2010 إلى 2020 وتمت مراجعة 64 دراسة تتعلق بتداخلين: التئام العظام وتسريع التئام الجروح. يظهر تحليل الضرر والفائدة في هذه الدراسة من خلال تطبيق النموذج الاحداث لمكعب باتيسون. اعتماداً على محاورها الثلاثة، يمكننا تقييم المعاناة الحيوانية، واحتمال الفائدة، وأهمية البحث. كان العدد الإجمالي للحيوانات المستخدمة في البحث 2685. الفئران، 51.6٪، والأرانب، 48.4٪، هي الحيوانات الأكثر استخداماً. تمثل الأبحاث المتعلقة ب التئام العظام حوالي 65.6٪، في حين أن الأبحاث المتعلقة بالتئام الجروح 34.4٪. كشف تقدير لجنة الخبراء لمعاناة الحيوانات أن 57.8٪ يعاني من معاناة حيوانية معتدلة؛ كان 39.1٪ معاناة خفيفة، و3.1٪ فقط تعرضوا معاناة شديدة. كشفت النتائج أن دراسات الأنسجة الصلبة تحصل على المزيد من الاستشهادات، 77.88٪ أكثر من الأبحاث المتعلقة بالأنسجة الرخوة. ومع ذلك، أظهرت دراسات الأنسجة الرخوة مزيداً من التوافق بين الدراسات قبل السريرية والسريرية. يجب بذل الجهود المستمرة للتأكد من أنه عندما تستخدم الحيوانات المختبرية في البحث، يتم تصميم كل دراسة بشكل جيد، وتحليلها جيداً، ونشرها بوضوح.

### معلومات البحث:

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### الكلمات المفتاحية:

تحليل الضرر، الفائدة، علم، الأنسجة، دراسة

بأثر رجعي

### معلومات المؤلف

الايمل: