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Pre-Clinical Animal Models in Dental Research

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ABSTRACT :

Advancement towards the implementation of newer treatment modalities in the field of dentistry is based on the evidences provided by the results of the pre-clinical animal trials. This needs careful selection of the animal model for the type of research involved, conditioning, nurturing and exposing to animal models to the research environment. This paper thoroughly explains on the animal samples to be chosen for the oral and dental experiments, procedures involved and ethical aspects in relation to the animal models used for research purposes.

Keywords: Animal models, pre-clinical, dental, research

Introduction:

The Nazi atrocities during World War II that allowed experiments on Jews and asocial persons alarmed the world to adopt Nuremburg Code that declared “any experiments on human should be designed and based on the results of animal experimentation". This was reinforced by Declaration of Helsinki (Revised in 1975) that stated "medical research on human subjects should be based on adequately performed laboratory and animal experimentation”. These laws upheld human rights in human experimentation and pledge the researchers to adhere to the protocols of research and experimentation.

Selection of right animal model for laboratory exercise is a vital phase in any preclinical dental research. It has to be based on genetic uniformity, biological properties, ease of adaptability of the model to experimental manipulation, transferability of information, ecological consequences, research animal care and management, its affordability and ethical responsibilities. Preferably, docile or non-aggressive animal analog has to be chosen for pre-clinical research. [1]

Animal models are advantageous in its ease of implementing and maintaining a constant or different experimental condition, conduction of terminal and invasive trials, reliable characterization of genetic coding due to complex pedigree system than humans, resemblance of certain organs and uncomplicated gathering of experimental data with analytical express ability. [2] Perhaps there exists limitation that not all human diseases can be reproduced and conclusions drawn from the animal research may not be always applicable in human subjects.[3]

Classification of Animal Models :

The animal models can be broadly classified as [4]

1. Experimental Model are the one in which the experimentally reproduced condition mimics a human disease.
2. Negative Model (Non model) are animal species in which a particular disease cannot be produced.
3. Spontaneous Mode is an animal species that has a disease which occurs naturally and mimics a human disease at least in some way.
4. Orphan Model an animal species that does not mimic a human disease

Animal models in Dental Research

3.1. Animals for caries and calculus research

Rodent species are ideal models for oral microflora, caries and calculus research. Hamsters could serve as primary model for caries research, as they are capable of harboring the cariogenic micro-organisms and form profuse amount of plaque that cause carious lesions. Gnotobiotic or germ-free rat are utilized to study maturation of enamel, cariogenicity of diet, bacterial involvement in caries process, anticaries efficacy of chemical agents and caries immunization.[5]

Ferrets are unique models for study of calculus, as they resemble human calculus and unlike rat or hamster it is not diet dependent.

Animal models for gingival & periodontal research

Dental gingival area in rats is similar to humans. But the anatomical structures of periodontal tissues and histopathological features of periodontal disease process in rodents are different from those of humans. Perhaps, they are resistant to periodontal disease progression and pathological processes can be induced by inoculating bacteria, or by giving a carbohydrate-rich diet or by fixing ligatures around the teeth. Continuous growth and migration of the teeth in rodents make them incompatible to histologically study the evolution of gingival and periodontal disease. However gnobiotic or germ-free rodents provide an opportunity to study the microbiological and immunological aspects of mono-infectious periodontopathogen bacteria of human origin.

Beagle dogs are the ideally the suitable periodontal disease models. Talbott(1899) was the first to identify periodontitis in these Mongrel dog and suggested that the occurrence of gingival recession and periodontal diseases progression is high in this species. It was noted that the organic composition and periodontal disease severity increased with ageing and etiopathology closely related humans. Their docile temperament and natural susceptibility to periodontal disease is added benefit for researchers. They differ in inflammatory response and bacterial population. Contrary to humans, the sub gingival connective tissue remains almost normal in dogs and conversion from gingivitis to periodontitis is not systematic. However, researchers can experimentally induced periodontitis by fixing ligatures around the teeth.[6]. Thus it is used to study of periodontal disease progression, guided tissue regeneration, tissue wound healing, and dental implants.[3]

Like humans, the non-human primates experience naturally occurring periodontal disease in later part of life and the lesions are asymmetrical. Ligature induced periodontitis around teeth and ligature-induced peri-implantitis follow similar destructive patterns like humans i.e, alteration of microbiological flora. Monkeys are suitable to evaluate periodontal regenerative procedures, especially since histometric analysis need to quantify the amount of new cementum, periodontal ligament and alveolar bone formed as the result of regenerative periodontal surgery. But the major disadvantage is that these animal species are expensive to obtain, housing, hard to handle and are highly infectious.

3.4 Implants & Biomaterial Research

Rat is the most commonly used species, in spite of its significant dissimilarities with human bone and its limitation in size making rats unsuitable for testing multiple implants simultaneously.[7] Larger animals such as sheep, goats and dogs are preferred for implant studies. The cylindrical implants of 4mm diameter and 12mm length are implanted in femur and tibia of the animals for analysis.[8] The long term implantation periods can be 12, 26,52 and 78 weeks in these animals, whereas rabbits is for 104 weeks (ISO 10993-6: 1994). However, through appropriate power calculations, not more than 4 implant in rabbits and 2 in other species at each implantation period can be placed.[9]

Non-human primates' suits well to research on implant associated changes. Lower rate of bone remodeling in a canine model may not be appropriate. However the monkeys are chosen in the secondary level and rats and rabbits in third level of implant experimentation.

3.4 Bone Remodeling Model

Screening of implant material is done on rabbits prior to testing them on larger animals or humans. The macrostructure and microstructure of rabbit bone is not similar to human bone, however bone mineral density & fracture toughness of mid-diaphyseal bone of rabbits are like humans. They have faster skeletal change and bone turnover, i.e, significant intracortica and haversian remodelling than in primates and other rodents. Smaller Implant size of 2mm diameter and 6mm length can be used in a healthy large female rabbit weighing between 3 to 3.5 kgs. The proximal femoral condyle of the rabbit that contains both cortical and cancellous bone is ideal location for implantation placement. It can provide adequate space for placing a larger implant (i.e., 6 mm diameter and 8 mm Length).

3.5 Oral Mucosal Caner

An ideal animal model to study oral squamous cell carcinoma (OSCC) should have the ability to induce oral cancer spontaneously. Thurman et al. reported a higher incidence (26.6%) of OSCC in male and female Norway rats. However, spontaneous OSCC are very rare in domestic and laboratory animals. Therefore genetic modified animal models through the addition of foreign genes (transgenic animals) or inactivation or deletion of genes (knockout animals) are often used.

Syrian hamster has the cheek pouch that anatomical and physiologically resemble human oral cavity. It has one pouch under the cheek muscles on each side of the mouth opens into the anterior part of the oral cavity and is associated with small salivary glands that produce both serous and mucous secretions. The pouches extend backwards along the oral cavity, but not as far as the pharynx. Histologically, the buccal cavity is lined with keratinizing squamous epithelium. Chemical carcinogenesis induction in hamster cheek pouch is of extensively used to research on OSCC.

Conclusion:

Globally rodents are used in 95% of the research. Larger animals like dogs, cats, primates are used between 0.5- 1% and less than one-quarter of one (0.25%) percent are non-human primates. The rest of the studies are conducted on rabbits, guinea pigs, sheep, pigs, fish and insects. Even though the animal disease pathogenesis is well understood, the similar diseases in human model are not. This suggests that animal disease model might not be

recognized as a true model. However, there are these unanswered questions (i.e., Are animals really necessary to biomedical research? What about animal's rights? Are there any alternative for animal research and how reliable are their results?)that still recommends the requirement of preclinical trial and choose of animals as biomedical research models.

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