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BIOCOMPATIBILITY TESTS- AN OVERVIEW

1. Dr Anupama Aradya, 2. Dr Sowmya H K, 3. Dr Padma Piriyaa S G, 4. Dr Madhumita Raju Pilla, 5. Dr Koduru Sravani MDS, 6. Dr Narahari Ranganatha MDS, 7. Dr Pradeep Chandra K, 8. Dr Shwetha E

Assistant professor Dept of ProsthodonticsJSS Dental college and Hospital, JSS Academy of Higher Education and Research, MysoreKarnataka-570015
Email id –dranupamavenu@gmail.com

Assistant Professor Department of Conservative dentistry and Endodontics
JSS Dental college and Hospital, JSS Academy of Higher Education and Research, Mysore

Post graduate student Department of Prosthodontics JSS Dental College and Hospital, Mysore

Post graduate Student Department of Prosthodontics JSS Dental College and Hospital, Mysore

Lecturer Department of Periodontics Dayanand Sagar College of dental sciences
Banglore, Karnataka , India

Reader Department of Oral and maxillofacial surgery Rajarajeswari dental college and Hospital Banglore, Karnataka , India

Senior Lecturer Department of Prosthodontics Dayananda Sagar College of Dental Sciences, Banglore

Senior Lecturer Department of Periodontology Sharavathi Dental College and Hospital Shimoga, Karnataka, India

Corresponding author-Dr Anupama Aradya, Assistant professor Dept of Prosthodontics JSS Dental college and Hospital, JSS Academy of Higher Education and Research, Mysore Karnataka-570015
Email id –dranupamavenu@gmail.com

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ABSTRACT

To ensure the health and safety of patients, all dental biomaterials must undergo screening assays to determine their biocompatibility. The objective of this review is to explain the framework of a test program as well as the worldwide biocompatibility requirements. The test program mandates that materials be structurally evaluated into four parts: general evaluations in pre-clinical and clinical settings for toxicity and local tissue irritation. There are different screening assay types available, and it is crucial to comprehend the benefits and restrictions of each form of assay so that they can be properly chosen and correctly understood. In terms of the chemical composition of dental materials, tissue engineering, stem cells, genetic transfer, biomaterials, and growth factor therapies, new scientific developments are now being developed.

These novel treatments increase the chances of restoring and regenerating oral tissues, but they can also expose patients to new risks. These new technologies must be demonstrated to be safe and not harmful to human health before being used in clinical settings. To assess these novel treatments, a systematic biocompatibility assessment and recommendations on assay selection are provided.

Keywords- Biocompatibility, Biomaterial, dental materials, In vitro tests, mutagenic reactions, Hypersensitivity

INTRODUCTION

Dental materials biocompatibility is a multiplex concept that draws on knowledge from biological science, patient hazard, and clinical research. Although ignored for many years, biocompatibility is now recognized as a fundamental requirement for any dental restorative material. Biocompatibility helps to ensure the wellbeing of patients and medical professionals. Its related issues can be connected to dentists' legal liability. It's crucial to understand the biocompatibility of frequently used dental materials to evaluate manufacturer guarantees made in their advertising. (1)

Rationale

The difficulty and technical issue of biocompatibility concern may seen beyond the range of performing dental practitioners. Although, these concepts have extreme ethical, community, engineering, and legal impact on prosthodontic practice. Dentists depend steadily on dental biological materials, due to the nature of prosthodontic treatments. This materials dependency makes biocompatibility concepts peculiarly pertinent to prosthodontists and other restorative dental specialists. (2,3) "The ability of a material to elicit an appropriate biological response in a given application." is known as Biocompatibility. (2,3)

Biomaterial is a non-living material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body. – ESB, Chester 1986.These materials are not biologically inert. Biocompatibility is a dynamic range process. It is a property of a substance and its environment.

HISTORICAL BACKGROUND

Hippocrates (Ethical treatment concept) was introduced in 460-377. Mid 1800's: For the first time Dentists tried new materials by placing them into patient's oral cavity. Fox: 'Fusible metal' – Bi, Pb, Sn were melted and poured into cavity preparation at 100°C. G.V. Black: tested many new restorative materials like early amalgams.

Today using human beings as research subjects without any previous testing or knowledge of biological properties of a dental material is unethical and illicit. Every new material needs to be inserted into a human for the 1st time at some point. Many alternative tests are being developed to reduce risks to humans.1960's: Current philosophy about testing biological properties of dental materials in systematic way to protect patients as number of materials increases. Public outcry against the use of nonconsenting humans as research subjects drove the development of regulations to protect humans in research. (4,5)

IRB (Institutional Review Boards)

IRB: Department of health and human services – agency federal government of the United States. It consists of the clinicians' committee, basic scientists' committee and lay persons. Control and supervise the testing of new materials in human beings. (6) Oversight for testing rests on: ISO (International Organization for Standardization): ISO 7405 and ISO 10993, ANSI (American National Standards Institute), FDA (Food and Drug Administration) and ADA (American Dental Association)

Requisites of biocompatible dental material

In the oral cavity dental materials should be harmless to all oral tissues including gingiva, mucosa, pulp, and bone. It should not contain any toxic, diffusible or leachable substance that can be released and enter the circulatory system, causing systemic noxious responses, including teratogenic or carcinogenic effects. The dental material should be free of agents causing sensitization or an allergic response in a sensitized patient. [5]

Adverse effects from dental materials

Toxicity

This is used for almost all dental materials as the first screening test. Materials may be efficient to release substances into patients' body and they could cause over toxicity. e.g.: early dental materials contained lead that leached into patient's body causing much risk to the health.

Inflammation

Complex response; involves initiation of host's immune system to prevent hazard. Results from allergy or toxicity, often inflammatory response precedes toxicity. Histologically: distinguished by tissue edema with inflammatory cell infiltration. Current biocompatibility research attempts to determine whether materials may cause or contribute to inflammation in the host even if no toxicity is evident.

Allergy

It is seen when the body specifically perceives a material as foreign and reacts disproportionately to the quantity of material present. Allergy involves T and B lymphocytes and monocytes. By the activation of antibodies to the material- Latex causes allergy directly. There are 6 types of allergic reactions (Table-1). In the 16 th century these toxic actions are dependent on the

dose- pointed out by Paracels. This principle quite applies. The concentrations required to activate an allergic reaction are individually different and they are much lower than those that cause toxic reactions.

Mutagenic reactions

Mutations - the material components alter the base-pair sequences of the DNA in cells. These alterations are called mutations. These reactions are caused by direct interaction between DNA and substance and indirectly by cellular processes alterations that maintain DNA integrity. Ni, Cu, Be in dental materials known mutagens, resin based materials also have some mutagenic potential. Mutagenicity does not imply carcinogenicity; many mutations are repaired. The form of material and route of exposure are important to mutagenic or carcinogenic response. (9,10)

Local & systemic effects of dental materials

Local effects might occur in the tooth pulp, periodontium, gingiva, root apex, or in the buccal mucosa or tongue, and excessive wear on opposing teeth from restorative materials. Local effects affect the function of the ability of substances that might distributed to these different sites, and their concentrations, and exposure times that range from seconds to years. (Table 2)

Systemic effects are dental materials gain access to the body via absorption and ingestion in the gut, vapor inhalation, release of material at the tooth apex, or absorption through the oral mucosa. Their distribution may occur by transport via lymphatic or blood vessels or by simple diffusion. These Response depends on the concentration of the exposure and duration of the exposure, the substance excretion rate and the exposure site (11)

BIOCOMPATIBILITY RELEVANT WITH DENTISTS

Dentists' possible concerns about biocompatibility can be assembled into 4 areas: patient safety, dental staff safety, regulatory compliance issues and legal liability

Safety of the patient

Preliminary concern is to prevent injuring the patient. Research has shown that biomaterials which are used by dental practitioners show safety risks to patients. Allergy to dental materials

such as resin-based materials, nickel or methacrylate, and to latex have been reported. Ask for patient's individual history.

Safety of the dental staff

Dental staff are chronically exposed. Classic example of dental amalgam, casting alloys, latex. Some resin components like tetra ethylene glycol Di methacrylate (TEGDMA), hydroxyethyl methacrylate (HEMA), and camphor quinone directly activate the immune cells

Regulatory compliance issues

Biocompatibility problems are firmly related to regulations that affect dental practice. Regulations have restricted and monitored the amount of amalgam in wastewater from dental practices and use of latex also.

Legal liability

These dental materials can affect the safety of dental auxiliaries, practitioners and patients assume a legal risk during usage of these materials. Financially and emotionally stressful to the practitioner. (12, 13)

RISK ANALYSIS

Risk is a combination of the likelihood of occurrence of harm (side effect) and the severity of that harm. To evaluate a risk each dental practitioner should have detailed knowledge about the composition of a material and its contaminants.

Factors to be considered in risk assessment of a material are the route of exposure, the timespan of the knowing contact with vital tissues, the threat possibly associated with the application And the constitution of the leaching material. (14)

ASSESSING BIOCOMPATIBILITY

There are 3 biocompatibility test types to assess the biocompatibility like in vitro tests, animal tests and usage tests, they have their own advantages and disadvantages (Table-3)

In vitro tests

First screening test to evaluate new material. It is performed outside living organisms (test tube, cell culture dish). Here material or extract is placed into direct or indirect contact with some biological system. Direct contact involves exposure of material/extract directly with the biological system. Indirect contact occurs through a barrier, (agar, a membrane filter, dentin)

Animal tests

The material is placed into an intact organism (usually mammal). Commonly: Mice, rats, hamsters, ferrets, guinea pigs are used. It is distinct from usage test; animal is exposed to material without regard to material's final use. There are different types like short-term, long-term systemic toxicity, exposure to intact or abraded membranes, immune sensitization , bone response and animal tests for mutagenicity/carcinogenicity

Usage tests

Performed in animals or humans. It requires the material to be placed in an environment clinically relevant to the use of material in clinical practice. If performed in humans is called clinical trial. Human clinical trials are considered "gold standard" of usage tests. (5,9-10)

USING DIFFERENT BIOCOMPATIBILITY TESTS TOGETHER

Three phases are generally recognized in the testing of a new biomaterial: primary, secondary and usage

Primary test

Performed initially in the testing of a new material, often in vitro in nature. E.g.: the first primary tests often conducted to evaluate a new casting alloy are in vitro cytotoxicity and mutagenicity tests. But primary tests might also include some animal tests to measure systemic toxicity. (15)

Secondary test

Always conducted in animals. E.g.: tests to measure dermal irritation, chronic toxicity, or response upon implantation are selected to observe the immune response. Secondary tests explore

beyond toxicity or mutagenicity issues such as allergy, inflammation, and other sublethal and chronic biological responses. (16,17,18)

Usage test

Testing on animals mimics a situation that is quite like a clinical one, particularly for systemic and cytotoxic qualities. (19) Ferrets, dogs, and even non-human primates are among the creatures tested. The length of testing is divided into short term and long term according to the ISO 7405 guidelines. The period is typically divided into different time intervals, ranging from 3 to 60 days or more.[20,21] A major barrier to adopting a short time can be the cost. Longer periods provide insight into the healing and regenerative processes, nevertheless.[22]

CURRENT BIOCOMPATIBILITY ISSUES IN DENTISTRY

Dental casting alloys:

Dental casting alloys play a prominent role in the treatment of dental disease. Alloys continue to be used as the principal material for fixed prosthetic restorations and will likely be the principal material for years to come. No other material has the combination of strength, modulus, wear resistance, and biologic compatibility that a material must have to survive long term in the mouth as a fixed prosthesis. (23)

Today ‘s practitioner may select from alloys based on palladium, silver, nickel, cobalt, and titanium, among others. Furthermore, alloys within each of these groups are diverse, and the practitioner faces a bewildering array of choices. Although uses for pure metals such as gold foil and platinum foil exist in dentistry, the main role for metals in dentistry has been in alloys. (24)

Alloys are used for fixed prostheses rather than pure metals because pure metals do not have the fore most important property of a casting alloy to its biologic safety is its corrosion, local tissues are attacked by much higher concentrations of released metal ions, Ni, Co can cause allergy and Beryllium is found to be carcinogenic

Latex:

6-7% of surgical personnel may be allergic to latex as estimated by FDA. Hypersensitivity was found in 3.7% of adult patients and 5.7% in pediatric patients.

Resins:

Risk is highest for dental personnel because of frequent exposure to unpolymerized materials. The allergenicity of methyl methacrylate is well documented, and the use of gloves is not effective in preventing contact because most monomers pass easily through gloves. Contact dermatitis and delayed hypersensitivity are seen.

Ceramics:

wear on restoration and opposing dentition. No long-term data on biocompatibility. (25)

Polyether impression materials:

Polyether impression materials have been observed to cause allergic reactions, and these show swelling, itching, and redness. After replacing the catalyst paste component that caused the allergy, no adverse reactions were seen. This was discovered via patch testing. Multiple allergy tests using polyether impression material, and its constituents (conducted between 2007 and 2009) were described in another retrospective investigation. Patch testing revealed a favourable response to base paste, mixed polyether impression materials, or the base component. (26)

Dental Implants

Due to their strong reactivity, zirconium and titanium quickly form layers of zirconium dioxide (ZrO_2) or titanium dioxide (TiO_2) when they are exposed to liquid or air. At the junction of the biological medium and this layer of metal dioxide, a boundary

the metal framework and stops further material deterioration. It results in the metal's passivation, which controls the implant's level of biocompatibility and biological reaction. Any breach in the oxide layer could result in corrosion of these metals and compromise their compatibility. (26,27)

CONCLUSION

We, being prosthodontists, depend more on materials that remain in intimate contact with living tissues for long periods. Since no material can be proven 100% safe, the decision to make use of a dental material in the oral cavity must balance the benefits and potential risks. Finally,

each dental practitioner must decide whether the benefits outweigh the risks for the patient under consideration. Technical tests and data can aid practitioners, but the decision is finally a philosophical one that should involve the patient, the manufacturer, and the practitioner.

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TABLES

Allergic Reactions	Types
Anaphylactic, Immediate atopic reaction	Type-I
hypersensitivity, Cytotoxic reaction	Type-II
immune complexes formation	Type-III
cell mediated, Delayed reaction	Type-IV
Stimulating antibody reaction	Type-V
Antibody dependent cell mediated cytotoxic reaction.	Type-VI

Table 1- Types of Allergic Reactions

Systemic toxicity	**Test duration**
Acute Less than	24 h
Subacute	Between 24 h and 28 days
Subchronic	90 days in rodents but not exceeding 10% of the lifespan of other species
Subchronic intravenous	14–28 days
Chronic	6–12 months

Table.2-Test duration for systemic toxicity

Test Types	Advantages	Disadvantages
In Vitro tests	• Relatively fast, inexpensive • Easily standardized • Used for large scale screening than usage/animal tests • Prevent the legal and ethical issues that surround the use of animals and human beings for testing.	• Potential lack of relevance to the in vivo use of the material. • Lacks complex coordination of systems. • Provides confusing results about ultimate biological response to the material.
Animal tests	• Ability to allow an intact biological system to respond to a material. • More relevant than in vitro test. • Shows important relation between clinical use of material and.in vitro environment	• Expensive • Difficult to control variables • Quantitative assessment is difficult. • Questionable relevance to humans.
Usage tests	• Human clinical trials are considered "gold standard" of usage tests. • Facilitates Food and Drug Administration (FDA) approval and market availability • Supports evidence-based medicine • Advances medical knowledge and treatment options • Contributes to public health advancements • Ensures Safety and efficacy of new treatments	• Risk of adverse reactions or side effects • Time-consuming and costly • Limited participant eligibility • Placebo control groups may not receive active treatment • Potential bias in study design or data interpretation • Regulatory complexities

Table 3- Advantages and disadvantages of different biocompatibility tests

Legends

Table 1- Types of Allergic Reactions

Table.2-Test duration for systemic toxicity

Table 3- Advantages and disadvantages of different biocompatibility tests