

Review paper

Know About Biocompatibility of Dental Materials: A Review

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Accepted 7th, October 2017

Abstract

Development in dentistry is characterized by an increasing number of new prosthetic materials. However, these materials interact with the tissues, producing changes in both the surrounding materials and tissues. They release substances into the oral environment to a varying degree. The aim of this review is to know the importance of biocompatibility of various dental materials used and the various spectra of biocompatibility test routinely practiced test. Articles are searched from the English literature available so far from the PubMed database, Google search and Science Direct from 1950 - 2017. Dental practice requires contact with restorative and auxiliary dental materials of different composition. The purpose of this article is to bring a general awareness to the dentist and other dental personnel and laboratory technicians about the biocompatibility of dental materials as leakage and transfer of potentially allergenic components of the materials carry the risk of hypersensitivity reactions.

Keywords: Biocompatibility, Dental Biomaterial, Dental Biocompatibility test.

INTRODUCTION

Dental practice requires contact with various restorative and auxiliary dental materials with different composition, these materials may cause leakage and release substances which are potentially allergenic components when interact with the tissues, may carry the risk of hypersensitivity reactions thus producing changes in both the surrounding materials and tissues with varying degree (Anusavice, 2008) (Padmaja, 2013). An overall estimate indicates the frequency of such adverse effects to occur in the 1:1000 to 1:10,000 of all dental treatments

(Mjor IA, 1992) i.e. 1 per 500 patients or of one patient per approximately 3.5 years of practice was reported in one study. Over 13,000 patients were examined for acute and long-standing adverse effects during a 2 week period.

But adverse effect depends on the type of practice and the materials used (Jacobson N, 1989). Prosthodontics and orthodontic treatments were somewhat over-represented compared with dental treatments of a general nature with involvement of many dental materials. Lichenoid reactions in the oral mucosa related directly to a restorative material were the most commonly reported side effects (Padmaja, 2017) (Cobos-Fuentes MJ *et al.*, 2009). Biocompatibility assessment is a planned and structured approach and it can't be rely on a single test. Possible harm evoked by the material, the

known data, and suitable biological and other test methods available must be taken into consideration. Modern regulatory concepts require for this purpose the services of experts to propose the appropriate set of required tests for a given material. The use of standards is generally emphasized because of better comparability of the data (Schmalz G, 1997).

Important Terms

1). Dental material is defined as a substance or combination of substances specially presented for use by authorized persons in the practice of dentistry or its associated procedures (Schedle *et al.*, 2007).

2). Biocompatibility is the ability of a material to perform with an appropriate host response in a specific situation. It can also be defined as the ability of a restorative material to induce an appropriate and advantageous host response during its intended clinical usage (Murray *et al* 2007).

3). Biomaterials are the materials which are able to function in intimate contact with biological fluids or living tissues with minimal adverse reactions in the body are called biomaterials. Materials can be categorized into three classes representing the type of tissue response they elicit chemically inert, bioresorbable or bioactive (Mahalaxmi, 2003). Biological side effects of materials used in dentistry are rare.

The concept of the ethical treatment of patients starts from the time of Hippocrates (460-377. B.C), however the idea that new dental materials must be tested for safety and efficiency before clinical use is more recent. G.V Black used patients to test many of his new ideas for restorative materials, such as early amalgams. In most cases, a committee of clinicians, basic scientists, and laypersons regulate and oversee the testing of new materials in humans. Using human- research subjects today without some previous testing or knowledge of biological properties of a material is unethical or illegal, (Anusavice, 2004).

Standards that regulate the measurement of biocompatibility

The first efforts of the ADA to establish guidelines for dental a materials came in 1926 when the scientists at the National Bureaus of Standards (now the National Institutes of science and technology) developed for dental amalgam. In ANSI/ ADA specification 41, three categories are described in the 1982: initial, secondary and usage tests. The ANSI/ ADA specification which governs biocompatibility testing in the United States is available from council on scientific affairs, American dental association. International standard ISO 7405 (1996) is entitled the Preclinical evaluation of biocompatibility of medical devices used in Dentistry –

Test methods for Dental Materials. This document was prepared with the World Dental Federation. It concerns the preclinical testing of materials used in Dentistry, and supplements ISO 10993. International standard ISO 10993 was formed to develop standards and the final document was published in 1992. International standard ISO 10993 entitled the Biological evaluation of medical devices is a combination and harmonization of International and National Standards and guidelines. (Andreas Schedle *et al.*, 2007). The primary goal is the protection of humans. This document has been continually updated, and is the overall guidance documents for the selection of tests, to be used for the evaluation of biological responses relevant to medical or dental material and device safety (ISO 10993, 1992).

METHOLOGY

The dental literature was searched from Google search and Medline/PubMed from 1950 to 2017 using various combinations of the following terms: Biocompatibility, Dental Biomaterial, Dental Biocompatibility test. After reviewing the titles and abstracts, reviews, case reports, original research and only the most relevant available article were included and the rest were excluded.

Need For the Biocompatibility

All artificial materials release substances into the oral environment and imply some risk of side effects and adverse reactions (Anusavice, 2004). The side effects reported seem to range from objective reactions based on observable phenomena, to more unspecific, general reactions that may or may not be associated with dental materials. Objective reactions could be either is intraoral such as lichen planus (local), gingivitis, ulceration and vesicles or extra oral such as eczema, erythema and blisters. Occupational reactions such as allergic contact dermatitis have also been reported in dental personnel associated with handling poor dental materials like amalgam as well as irritative contact dermatitis caused by wet work (OMCC/UNEP/WHO. 2008). Possible adverse reactions encountered with dental materials are (Andreas Schedle *et al.*, 2007.)

1). Toxicity

Materials may be capable of releasing substances into a patient's body and the release of certain substances in adequate amounts can cause overt toxicity.

2). Inflammation

Inflammatory response involves the activation of the host's immune system to ward off some threat. Inflammation may result from toxicity or from allergy.

Pulpal and periodontal diseases are largely chronic inflammatory responses to long term infections.

3). Allergy

Allergic responses occur when the body, specifically recognizes a material as foreign and reacts disproportionately to amount of material. The reaction involves all dimensions of the immune system.

4). Mutagenicity

Mutagenic reaction results when the components of a material alter the base-pair sequences of the DNA in cells. These alterations are termed mutation. It can be caused by direct interactions between a substance and DNA or indirectly by alterations in cellular processes that maintain DNA integrity, genotoxicity, the alteration of the genome DNA of somatic or germ line cells increasing the risk of cancer or inheritable defects.

5). Immunotoxicity

Immunotoxicity lies in the boundaries between toxins, inflammation, allergies and mutagenic reactions. It is based on the principal that all alterations in the cells of the immune system by material can have significant biological consequences. It may also result from material causing either an increase or decrease in cellular function. A dental material has both systemic and local effects in the body. (Andreas Schedle *et al.*, 2007.)

BIOCOMPATIBILITY TESTS

Various preclinical biocompatibility test system has been introduced to evaluate the risk factors and these tests are categorized on the basis of their applicability levels evaluation of the potential risk of dental materials, (ISO 7405 and 10993-5), (Anusavice, 2004). The following sequence was adopted by the ISO (1984) in Technical Report 7405:

A. Initial Tests: Includes cell culture tests, hemolytic tests, systemic toxicity tests and test estimating teratogenic and carcinogenic effects and potential.

B. Secondary Tests: Cover implantation tests, skin and mucous membrane irritation tests and sensitization tests.

C. Usage Tests: Take into account the manner in which the materials are intended to be used in clinical practice (Anusavice, 2004).

The most common progression is from primary to secondary to usage tests, but any test may be performed at any time in the development of a material, depending

on the problems that are encountered (Andreas Schedle *et al.*, 2007.)

IN VITRO TESTS

Direct cell culture and culture extract testing or barrier screening assays

In this method dental materials are placed directly into cells in a mono-layer culture, over a short period of time. Mouse fibroblast or human epithelial cells are used for test, (Leirskar J, 1981), (Beltes P, 1995).

Agar Diffusion Testing

The test material is placed on top of the agar layer, and the cells are incubated. A zone of malformed, degenerative or lysed cells under and around the test material indicates cytotoxicity, (Peter E. Murray, 2007), (Guess WL, 1965), (Grasso P, 1973).

Filter Diffusion Testing

In this method, a cellulose acetate filter having 0.45 um filter paper is used. Cells are grown on one side of the filter and the test material is placed in contact with the opposite surface of the filter. Thus, any leachable substances must diffuse through the filter pores to exert any cytotoxic effects on the cells, (Wennberg A, 1976)

Dentin Barrier Testing

It is also called a model cavity method. It stimulates in vivo oral environment by placing a bovine dentin disk between the pulpal fibroblast and the test materials. It helps to identify specific components which may be responsible for pulpal effects through the dentin. It may help to identify compounds that repress or intensify the cytotoxic effects, (Tyas M, 1977)

Ames Test

It is a special culture agar is used which is histidine deficient. Genetically altered bacteria are used as test organisms which cannot grow and form colonies on the histidine deficient medium. If the test material is mutagenic, the bacteria will begin to grow. Number of colonies formed indicates the degree of mutagenicity.

Style's Test

It is a modification of Ame's test that uses normal fibroblasts cultured from baby hamster kidney. The presence of a carcinogen can be identified upon the addition of the substance, if carcinogenic, turns the material into quasi-cancerous state (Sakaguchi RL, 2012).

Micronucleus Test

It is genotoxicity test used for the detection of micronuclei in the cytoplasm of the interphase cells. In the test the experimental material is exposed to cell cultures of human or rodent origin with or without an exogenous source of metabolic activation.

The MTT Assay

It is a colorimetric assay for measuring the activity of cellular enzymes. It uses tetrazolium dye, MTT for measuring the cellular metabolic activity, cytotoxicity. The test is done in the dark since the MTT reagent is sensitive to light, (Bernas T *et al.*, 2002).

Cell Lines

A number of cell lines has been used for cell damage caused by dental materials. The human cell line test is more sensitive to these tests than animal cell lines. Human pulp stem cells and periodontal ligament stem cells are used. (Murray PE, 2000).

Tooth Slice Culture Assay

This assay preserves the vitality of the tooth and hence a possible extrapolation of a clinical scenario is permissible. The method is a satisfiable surrogate for animal and human testing. (Murray PE, 2000). In comparison to the above methodologies, a cytotoxic impact on the pulpal tissue, growth factors, stem cell and gene therapy could be precisely evaluated, (Sloan AJ, 1999), (Melin M, 2000). This method largely inhibits the confounding factors that would otherwise have a bias; the cost factor is glaringly reduced.

Animal Usage Assay

The ISO 7405 guidelines recommended preclinical testing in adult nonhuman primates. Biological testing relies heavily on animal experimentation. Before a dental material can be used clinically, it must always be tested to establish its systemic and cytotoxic properties. Animal experimentation: Rabbits – ear, skin, pyrogen; Guinea Pigs – skin; Mice – genotoxicity. Pig – implant; Bacteria – genotoxicity; Dogs and ferrets, (Rowan AN, 1997)

Implantation Test

Materials are implanted subcutaneously, intramuscularly or in the bone of an experimental animal. The test material may be directly injected or implanted (either directly or within silicone or polyethylene tubes) into various tissues, such as the subcutaneous connective tissue, muscle or bone of rats, rabbits, guinea pigs, hamsters and ferrets (Torneck 1961, Thomas *et al.*, 1985,

Tagger & Tagger 1986, 19, Maher *et al.*, 1992, Pertot *et al.*, 1992, Tassery *et al.*, 1997, Kolokuris *et al.*, 1998).

After different periods of implantation of the material in the tissues, the adjacent tissue is investigated macroscopically and microscopically to check for the reactions elicited.

Irritation Tests

Estimate the local irritation potential of materials using site skin or mucous membranes, usually in an animal model. Primary skin irritation test is the test in which material is applied directly to intact and abraded sites on the skin of a rabbit/guinea pigs. After a 24-hour exposure, the material is removed and the sites are scored for erythema and edema. A mucous membrane irritation test determines if a material causes inflammation to mucous membrane. The test materials are placed in contact with the cheek pouch, tissue or rabbit oral tissue. After several weeks of contact tissue reactions are recorded. These studies often use extracts rather than the material itself. (Schmalz G, 2000). The Slug Mucosal Irritation assay (SMI) assay can predict the local tolerance of solids, semi-solids or liquids. The irritation potency is predicted based on the total amount of mucus produced during the repeated 30-min contact periods. The mucus production is expressed as a % of the body weight of the slugs.

Maximization Test

Materials are injected intradermally to test for development of skin hypersensitivity reactions. Immuno potentiator can be used (FCA-Freund's complete adjuvants). 7 days later, the same substances are applied topically (adhesive patches) to the same site. If hypersensitivity developed from initial injection, the patch will elicit an inflammatory response. Skin patch test results in a spectrum from no reaction to intense redness and swelling (Swetha, 2015).

Usage Tests

The test material is placed in an environment relevant to the use of materials in clinical practice. The test is performed in animals (larger animals with anatomy closely resembles that of humans) and human. If the test is performed in humans it is called clinical trial rather than a usage test, (Mahalaxmi, 2003). The gold standard of usage test is "clinical trials" that are performed in the humans.

Pulp Dentin Test

It is carried out on teeth of experimental animals. The teeth are removed and histologically prepared and pulps are microscopically evaluated.

Endodontic Usage Test

The material is placed in the root canals of the animal Modes after root canal preparation. Histological evaluation of the apical tissues is done.

Intraosseous Implant Test

Materials used for dental materials are inserted into the jaws of test animals. The tissue reaction is assessed histologically.

Clinical Testing

The ideal method to evaluate the biocompatibility of a material would be to test it on human subjects, but because of legal and ethical issues this is not possible. In order to protect human, a test a material can be tried on humans only if it clears the vitro, animals and usage tests.

Once a material passes through the in vitro and animals test an IND application (notice of claimed investigational exemption for a new drug) is submitted to FDA for approval. After the material is approved by FDA, it can be subjected to the following three phases of clinical trial (Mahalaxmi, 2003).

1). Phases I Trials

Materials are tested in a few healthy subjects after obtaining informed consent Phases II Trails: Materials is tested in a small group of patients.

2). Phases III Trails

Materials are subject to large scale study. Data obtained from these trails is the submitted to FDA in NDA (new drug application). The FDA then designates the test materials as "complete" or "incomplete".

3). Phases IV Trials

Reports regarding any allergies, interaction with other materials and the amount of materials circulated must be reported to the FDA at timely intervals.

To protect human health, clinical testing can only be conducted with test materials and treatments that have successfully passed the first three phases of biocompatibility testing recommended by ISO guidelines. The clinical testing of restorative materials is evaluated according to the United States Public Health Service Or Ryge criteria prior to commercial sales.

MATERIALS ASSOCIATED WITH ADVERSE REACTIONS

Polymer based materials (PMMA)

It can to elicit irritation, inflammation and allergic reaction. Reactions to resin-based materials are swelling, sores or necrosis of the oral mucosa (Rahul Bhola, 2010).

- i). Heat cured acrylics are well tolerated by gingival tissues as compared to cold cure resins.
- ii). PMMA resins may leach 0.1 to 5% of the residual monomer and additives mainly MMA and formaldehyde contributing to localized reactions.
- iii). EGDMA is a water- soluble monomer common in composite and bonding materials as a cross linking agent. It is shown to be both an allergen and cytotoxic.
- iv). TEGDMA shows a major cytotoxic potency as compared with other resin monomers and additives and it has a great potential to degenerate DNA.

It is evident that formaldehyde, which is the by-product from polymerization leaches from several composite resins in a long period after polymerization. In filings with an oxygen-inhibited surface layer, the leakage seems to be more prominent since the inhibited meth acrylic molecule will react with water from the saliva creating formaldehyde. This substance is known to cause allergies as well as toxic/genotoxic reactions.

Latex

Adverse reactions in 3.7% of adults and 5.7% of paediatric patients were associated with latex gloves. 8.8 % of adult patients who experiences hypersensitivity reactions used latex gloves at work. Hypersensitivity to latex causes dermatitis of the hands. Asthmatic reactions and other respiratory reactions have also reported to components of the latex that are released in the air and carried by the powder coating on many latex products, (Andreas Schedle *et al.*, 2007), (Anusavice, 2004).

Amalgams

Biocompatibility of amalgam is caused by the corrosion products released while in service. Corrosion depends on the type of amalgam whether it contains the γ_2 phase, and its composition.

- i). In cell culture screening tests, free or non reacted mercury from amalgam is toxic. With the addition of copper, amalgams become toxic to cells in culture, but low copper amalgam that has set for 24 hours does not even inhibit cell growth.
- ii). Implantation tests show that low copper amalgams are well tolerated, but high copper amalgam causes severe reactions when in direct contact with tissues.
- iii). In usage tests the response of the pulp to amalgam in shallow or deeper but lined cavities are minimal, and amalgam rarely causes irreversible damage to the pulp,

(John M, Powers, 2002).

iv). It is recently reported that Mercury seems to risk factor for Alzheimers disease, (Paolo D, Pigatto, 2017)

Metals and its Alloys

A number of different alloys are used in dentistry for fillings, fixed and removable prosthetic works, orthodontic devices and dental implants. Non-precious dental alloys like Co-Cr and Ni-Cr alloys are used more frequently.

- i). Metal and alloys release metal ions that cause mutagenic and carcinogenic.
- ii). Metal ions such as Palladium, gold, Indium or platinum causes less effect. Pd-Cu alloys show allergic reactions, while such symptoms do not show with other Pd alloys, (Anusavice, 2004), (SI-Rong YU, 2004).

Casting Alloys

- i). In Cell culture test these alloys appear to be more cytotoxic than traditional high copper amalgams.
- ii). In Implantation test, gallium alloys causes significant foreign body reactions. (John M. Powers, 2002).

Studies have shown that the increased cell density reduced the sensitivity to most metal ions. Cell density affects cytotoxicity to the behavior of each metal ion differently, (John C. Wataha, 2000),

Implant materials

Reactions to ceramic implant materials, most ceramic implant materials have very low toxic effects on tissues, because they are in oxidized state and are corrosion resistant (John M. Powers, 2002).

- i). The corrosive products of dental implant have been implicated in causing local pain and swelling in the region of the implant without infection. Hexavalent chromium ions are released from implant materials which causes cytotoxicity. Titanium has been used successfully as an implant material. However, in combination with different metals, Titanium can form strong galvanic cells, so caution is necessary when combining titanium with other alloys. Ti alloys without Ce and without 0.3% Ce does not have toxicity (SI-Rong YU, 2004). Precious metals (An, Ag, Pd) in combination with titanium practically do not form galvanic currents, while in combination with Cr-Mo and Ni-Cr, weak galvanic currents are formed. Coupling of Gallium alloys to titanium may result in increased galvanic corrosion and cytotoxic responses. SLA (sandblasted and acid etched) titanium surfaces show good biocompatibility for differentiated PDLSCs which is important for application of these cells in per implant nerve tissue engineering through which they are expected to improve the osseous perception of dental

implants. Considering that proinflammatory cytokine levels in GCF around ceramic abutments are lower than titanium ones, ceramic abutments are preferred for clinical usage. (Negahdari R, 2017).

Nickel

It is a moderate allergen, as detected by patch testing's for contact allergies. Messer and Lucas investigated different nickel alloys. Some of the alloys showed a high inclination towards corrosion and cytotoxicity, although such results were not shown by all nickel alloys. But no evidences that the individual patients are at a significant risk of developing sensitivity solely attributed to contact with nickel containing dental appliances and restoration (Jia W *et al.*, 1999).

Beryllium

It is used in Ni-Cr alloys in concentrations of 1 wt% to 2% to increase the cast ability of these alloys and lower their melting range. Beryllium is documented carcinogen in either the metallic or ionic state. Beryllium containing particles that are inhaled and reach the alveoli of the lungs may cause a chronic inflammatory condition called berylliosis, (Anusavice, 2004). It occurs in individuals with a hypersensitivity reactions to the beryllium and may occur from inhalation of beryllium dusts (from grinding or polishing alloys), salts, or fumes, such as those encountered when casting beryllium containing alloys. (Andreas Schedle *et al.*, 2007).

Dental Bleaching Agents

It can be verified through functional and morphological alteration of macrophages. In vitro studies have demonstrated that peroxides can rapidly (within minutes) traverse the dentin in sufficient concentrations to be cytotoxic. The cytotoxicity depends to a large extent on the concentration of the peroxide in the bleaching agent. In vivo studies have demonstrated adverse pulpal effects from bleaching. Bleaching agents will also burn the gingiva if the agent is not sequestered adequately in the bleaching tray. Some investigators have reported that 30% hydrogen peroxide is cytotoxic while Sodium per borate is a biocompatible product as it caused neither morphological nor functional alterations in macrophages (Kattyenne Kabbaz Asfora, 2005)

Cements

- i). Eugenolis known to be cytotoxic and allergic substance.
- ii). Calcium hydroxide cements containing resin cause mild to moderate cytotoxic effects in tissue culture in both the freshly set and long standing set conditions. When resins are incorporated, calcium hydroxide compounds

become less irritating and are able to stimulate reparative dentin bridge formation more quickly than the calcium hydroxide suspension alone.

iii). In vitro screening test indicates that ZNPO₄ cement causes strong to moderate cytotoxic reactions that decrease with time, (Espelid I, 1999). In usage test in deep cavity preparation moderate to severe localized pulpal damage is produced within 3 days. The PH of the set cement approaches to neutrality after 48 hrs.

iv). Tissue culture test of cytotoxicity of freshly set Zinc polyacrylate and completely set cements has correlated with the release of zinc and fluoride ions into the culture medium and with reduced PH. Poly acrylate cements evoke a pulpal response similar to the cause by ZOE, with slight to moderate response after 3 days. Reparative dentin formation is minimal with these cements and they are recommended only in intact dentin in the floors of the cavity.

v). In vitro eugenol from ZOE fixes cells depresses cell respiration, and reduces nerve transmission with direct contact.

The effect of eugenol is dose dependent and diffusion through dentin dilutes eugenol by several orders of magnitude, in usage tests ZOE caused slight to moderate inflammatory reactions within the first week. This was reduced to mild chronic inflammatory reactions, with some reparative dentin formation (within 5 to 8 weeks), when cavities were deep. (John M. Powers, 2002).

Pulp sensitivity following cementation with zinc phosphate and glass ionomer cements showed less sensitivity to zinc phosphate and glass ionomer during the first 2 weeks, but after 3 months there were no differences. Resin modified glass ionomer cements are dental restorative materials of glass ionomer family, this means that they contain basic ion leachable glass powder and a water- soluble polymeric acid such as poly (acrylic acid), (John w. Nicholson, 2008). The biocompatibility of resin modified glass ionomer is less as compared to conventional glass ionomer. Glass ionomer cement provides a complete seal against bacterial micro leakage through all time intervals. No serious inflammatory reactions were observed in the pulp. Ceramic reinforced glass ionomer shows superior biocompatibility compared with conventional glass ionomer, (Tamilselvam S, 2013)

Estrogenicity

It is the ability of a chemical to act as the hormone estrogen does in the body. The concern about estrogens in dentistry center around a chemical called Bisphenol A (BPA) which is a synthetic starting point for all Bis-GMA composites. BPA was as early as in the 1930s recognized for its estrogenic effects. In vivo and in vitro studies have confirmed this, but few studies have examined the estrogenic effects of BPA derivatives.

Because of its character to imitate natural estradiol, and its weak affinity to estrogenic receptors, BPA and bis-GMA might be involved in the etiology of reproduction- and developmental disturbances and malignity. Studies have shown that BPA probably is a thousand fold less potent than natural estrogen. There are evidences that BPA and BPA di methacrylate may act on the estrogenic receptors- in the cells.

MTA and Portland Cements

They are bioactive materials. MTA produces calcium hydroxide as a by-product of the hydration reactions. The similarity of action of both MTA and Portland cement to calcium hydroxide had been postulated, (Josette Camilleri, 2006),

Impression Materials

In dental practice, different materials and impression techniques are used, according to clinical needs. During impression taking, the materials come in contact with the cells of theoral mucosa. Small fragments of the polymerized materials can remain entrapped inside the gingival sulcus or underneath a mucosa- connective tissue flap. Such materials must be therefore inert to avoid structural and functional alterations of tissue cells. Hence the need to use biocompatible dental materials, (Chiara Coppi *et al.*, 2005)

Denture Adhesives and Soft Tissue Liners

Plasticizers, incorporated into some materials to make them soft and flexible, are released in vivo and vitro. Cell culture tests have shown that some of these materials are extremely cytotoxic and affect number cellular metabolic reactions. In animals, several of these materials have caused significant epithelial changes, presumably from released plasticizers. In usage test the effect of the released are probably often masked by the inflammation already in tissues onto which these materials are placed. Denture adhesives have been evaluated in vitro and show severe cytotoxicity.

Phthalates

In dentistry, phthalates are mainly used as plasticizers an indenture soft-lining material, denture to a minor extent and in some orthodontic appliances phthalates are not chemically bound to the polymeric matrix, but is situated between the polymers, it has a great potential to leach or migrate out into the surrounding atmosphere. When used in prosthetic or orthodontic appliances, the patients will be exposed to these substances directly through the mucosa and saliva. Some phthalates are known to have estrogenic effect, and such have the ability to interfere with reproduction and create damage to the fetus. The

main concern of phthalates is the potency of causing endocrine disruptions, mainly adverse effects on reproduction and development. No phthalates have been shown to be mutagen or genotoxic.

INTRACANAL DRUGS

Sodium hypochlorite

A 0.5% sodium hypochlorite (NaOCl) solution, also known as Dakin's solution Sodium hypochlorite is an effective antimicrobial against endodontic flora with some tissue-dissolving properties: NaOCl is highly toxic in high concentration and tends to induce tissue irritation on contact, (C. H. J. Hauman, 2002).

Ethylene Diaminetetraacetic Acid

The disodium salt of ethylene diaminetetraacetic acid (EDTA) is generally accepted as the most effective chelating agent and lubricant (if in the correct vehicle e.g. RC-Prep, Premier Dental Products Co., Pennsylvania, USA) in current endodontic practice leakage of EDTA to periapical tissues during root-canal preparation may inhibit macrophage function, and thus alter the inflammatory response in periapical lesions. EDTA has been shown to have weak antibacterial and antifungal properties, (C. H. J. Hauman, 2002).

Chlorhexidine

Chlorhexidine is a cationic bisbiguanide with optimal antimicrobial action ranging from pH 5.5 to 7.0. It is active against a wide range of microorganisms, such as Gram-positive and Gram-negative bacteria, bacterial spores, lipophilic virus, and yeast. Agarwal *et al.*, (1997) found that chlorhexidine rapidly disrupts the cell membrane of both crevicular and peripheral blood neutrophils at concentrations above 0.005% within 5 min, indicating that its inhibitory effect on neutrophil function is mostly due to its lytic properties. In a study by Yesilsoy *et al.*, (1995) he found that assessed of the short-term toxic effects of chlorhexidine in the subcutaneous tissue of guinea pigs and found a moderate inflammation present after 2 days, followed by a foreign-body granuloma formation at 2 weeks, (C. H. J. Hauman, 2002)

Many materials in dental surgery, biocompatibility concerns are not as great a concern as other issues, such as long-term degradation, mechanical strength problems, and prevention of secondary caries. The potential exists for adverse tissue responses to synthetic materials used in repair, augmentation, and repair of natural tissue structures should also be considered. As new materials and repair techniques become available and the sophistication of cell-level and subcellular response evaluations increases, the concerns to be

addressed and the methods to be used may change, (Turkkan S *et al.*, 2017).

BIOLOGICAL RESPONSE IN THE DENTAL ENVIRONMENT

Several aspects of oral anatomy influences the biocompatibility of dental restorative material have profound influences on the biological responses to material and all its sites of interface between material and tissues in dentistry. A number of factors need to be into account when estimating adverse biological reactions to Prosthodontics' materials. Among these include the type, form, contour, extent of prosthesis, any medication used by the patient, salivary flow rate, xerostromia, oral hygiene, and quality of fit and function of prosthesis. Biological films, pellicles of salivary origin will also accumulate on the materials they differ in composition depending on the material and on the properties of the patients' saliva.

Several factors that affect the biocompatibility of the material

i). Various metal corrosion or other types of material into degradation

Corrosion results in the release of substances from a material into the host. The release can take many forms and many forms and may be many factors biocompatibility of the material depends to a large degree on the degradation process. Corrosion is determined by biological environment in contact with material which may be specific or common to all individuals and the surface characteristics affects the biocompatibility.

ii). Surface

It is the part of material that the body "sees", the surface composition, roughness, mechanical properties, and chemical properties are critical to biocompatibility of the material.

Eg: The chemical characteristics of titanium oxides promote osseointegration of bone with many titanium alloys. Similar responses seen in some ceramics, it allows osseointegration and also promotes bone formation. Surface may also negatively affect the biological response. A rough surface material promotes corrosion, adherence of bacteria, periodontal inflammation or dental caries. The surface characteristic of a material is different from that of its interior region.

Control of the adverse reaction: Correct handling of resin-based materials is crucial to achieve desirable results. Proper material handling methods directed to reduce leakage and degradation and minimize direct exposure of unpolymerized material.

In the treatment of patients with confirmed allergy to a specific substance, materials containing that substance should be avoided. A clinical challenge is that acrylic monomers do cross-react; this means that sensitizing induced by one monomer may extend to other monomers as well. The patients become multi-allergic and cannot be exposed to any monomers in resin based materials. During treatment of patients with known hyper sensibility to dental materials, precautions should be taken. During therapy where the handling of resin-based materials are required, the aim of the treatment should be to minimize unnecessary direct exposure of highly reactive, unpolymerized materials, as well as lower the possibility of monomer leakage during the first days after filling therapy. Use of rubber-dam will act as a barrier, and prevent monomers from bonding and composite to come in contact with the oral mucosa. Some precautions decrease direct exposure of unreacted monomers should be taken on every patient. When filling therapy is indicated, the dentist should avoid direct exposure of unpolymerized materials to the oral mucosa of the patient. Rubber-dam may act as a physical barrier to prevent contact, (Anusavice, 2004).

Resin-based bonding materials are low viscous, therefore attention should be directed to amount of bonding material applied, and use of suction to reduce vapors. When use of a matrix system is required, this should be fitted tightly around the tooth, to prevent cervical leakage and decrease the risk of oxygen inhibition. Correct light curing results in decreased amount of unpolymerized reactive monomers in the composite filling or luting cements. The compost should be placed in several thin layers, to ensure polymerization in the deepest parts. Sufficient light curing also depends on light intensity, distance between the monomers and the light source, curing time and material. The light intensity of the curing lamp should be at a minimum of 400 mW/cm². After curing of the last layer of compost, polishing is important to remove the oxygen- inhibited layer at the surface. During therapy with some glassionomer composites, application of coating has been recommended from a Norwegian study to decrease leakage.

DISCUSSION

Biocompatibility is defined as the ability of a material to function in a specific application in the presence of an appropriate host response (Williams 1987). According to EN 1441 (European Committee for Standardization 1996) biocompatible materials must be free of any risks. Appropriate host response means no (or a tolerable) adverse reaction of a living system to the presence of such a material. An adverse reaction may be due to the toxicity of a dental material (Polyzois GL, 1994). Toxicity may be regarded as one reason for non-biocompatibility

of a dental material. The toxicity of a dental material can be evaluated by in vitro tests, animal experiments and clinical trials. There exist a variety of different in vitro test methods. It is thus impossible to biologically characterize the materials by a single test method alone and their properties need to be investigated by a battery of various in vitro and in vivo tests in a structured approach.

Autian (1970) was the first to propose a structured approach as a concept consisting of three levels: Nonspecific toxicity (cell cultures or small laboratory animals); Specific toxicity (usage tests, e.g. in subhuman primates); Clinical testing in humans. According to Autian (1970) the term 'nonspecific' refers to test systems which do not reflect the application of a material in a clinical situation while- the term 'specific' applies to the use of biological models simulating the actual clinical use of the material. The most widely used biological systems for toxicity screening of dental materials are cell cultures. Cell cultures for toxicity screening of dental materials are valuable tools for understanding their biological behavior, if the limitations of the methods take into consideration, especially concerning the interpretation of the results.

Barret *et al.*, showed that NiTi arch wires released more Ni than their stainless steel counterparts (Barrett RD *et al.*, 1993). Amini *et al.*, reported that the presence of fixed orthodontic appliances leads to an increased concentration of metal ions in salivary secretions. In vitro test systems for genotoxicity can be differentiated into prokaryotic (e.g. Ames test) and eukaryotic assays (e.g. DNA synthesis inhibition test (DIT), (Arndt M *et al.*, 2005), (Jacobson N *et al.*, 1989), (Petoumenou E *et al.*, 2009).

The practitioners' potential concerns about biocompatibility can be organized into four areas: safety issues for the patient, safety issues for the dental team, compliance issues, and liability. This review article will bring a general awareness to the dentist and other dental personnel and laboratory technicians about biocompatibility of dental materials and applications of various tests and possible adverse reactions to a wide range of dental materials, e.g. metals, alloys, polymers and cements

CONCLUSION

Biocompatibility is a complex and rapidly evolving research area that may seem beyond the purview of practicing dentists. These issues have profound ethical, social, technical, and legal implications for dental practice. The technical issues of biocompatibility may seem beyond the scope of most practicing dentists, knowledge of these issues is fundamentally important to ensure the health of patients, dental staff members (including laboratory personnel), and practitioners themselves. Measuring biocompatibility is a complex process that involves in vitro and in vivo tests. These tests contribute to understanding biologic responses to a

material but cannot define the material biocompatibility with 100% certainty.

CONFLICT OF INTEREST

None.

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