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Dental Outlook in Transplant Patients

Transplant Hastalarında Diş Sağlığı

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ABSTRACT

In today's scenario dentists are more likely to encounter transplant patients for dental care as annually more than 100000 transplantations occur worldwide. Untreated dental disease represents a potential risk for infection and deprived quality of life in transplant patients. These patients are prone for many oral diseases and minor negligence can lead to fatal consequences. This paper aims to provide an insight of transplantation immunology, common oral manifestations and an effective treatment plan depending on the medical condition of the patient In this review, a method used for searching data includes various internet sources and relevant electronic journals from the Pub Med and Medline databases with limits and keywords according to the precise vocabulary "Medical Subject Headings" (MeSH) from January 1984 to January 2012. Prophylactic and therapeutic dental treatment is essential at the primary level to prevent serious infections from oral sources during immunosuppression and the elective dental treatment should be preferably planned during the stable post transplantation period. On the basis of the literature review it is recommended that the dental care in these compromised patients has to be modified to meet their medical status and also depending upon the type of transplantation.

Key words: Transplantation, transplant immunology, oral manifestation, dental management.

ÖZET

Dünya geneline baktığımızda her yıl 100000'den fazla transplantasyon yapılmaktadır. Dolayısıyla bu günün beklentisi, diş hekimlerinin her geçen gün transplant hastalarının diş bakımlarıyla daha fazla karşılaşacakları üzerinedir. Henüz tedavi edilmemiş diş hastalığı, enfeksiyonların ortaya çıkmasında risk faktörüdür ve transplant hastalarının hayat kalitelerinde düşüşe neden olmaktadır. Bu hastalar

birçok farklı oral hastalığa yakalanmaya meyilli haldedirler ve küçük bir ihmal bile ölümcül sonuçlara neden olabilmektedir. Bu makalenin amacı; transplantasyon immünolojisine, yaygın oral belirtilere ve hastaların sağlık durumlarına bağlı olarak etkili bir tedavi uygulamaya yönelik yaklaşımları belirlemektir. Bu derlemede, gerekli datalara ulaşabilmek için farklı internet sayfalarının yanı sıra Pub Med ve Medline adreslerine 'Medical Subject Headings' ifadesi girilerek 1984 Ocak ayından 2012 Ocak ayına kadar yayımlanmış elektronik dergilerdeki makaleler tarandı. Profilaktik ve terapötik diş tedavileri, immün sistemin baskılandığı durumlarda oral kaynaklı ciddi enfeksiyonlardan primer korunma için gereklidir ayrıca transplantasyon sonrasında da hastalara özel uygun oral tedavi stratejisi belirlenmelidir. Literatür değerlendirmesine göre böyle durumda olan hastaların oral bakımları, hastaların tıbbi durumlarına ve transplantasyon tipine bağlı olarak belirlenmesi gerektiği önerilmektedir.
Anahtar kelimeler: Transplantasyon, transplant immünoloji, oral belirti, dental yönetim.

Introduction

Advances in the medical field have increased the number of transplant recipient and yearly more than 100,000 transplantations occur worldwide with kidney transplantation to be the maximum[1]. This scenario has increased the dentist and transplant patient's interaction and their special dental needs. It has been noted that transplant recipients exhibit better quality of life than the transplant candidates who have not yet received the graft[2]. Precautionary measures should be adapted so that the quality of life is not jeopardized by dental problems, particularly due to infections, prior to and following the transplant. Success in the management of these patients requires health status information and appropriate preventive and therapeutic protocols. These patients with markedly greater comorbidities demand meticulous pre and post-transplant dental care.

The aim of this article is to systematically review the published literature on the oral manifestations and the dental management of transplant patients.

Material and Methods

In this review, a method used for searching data includes various internet sources and relevant electronic journals from the Pub Med Medline databases and the COCHRANE Central register from January 1984 to January 2012. The search approach was based on the evidence based medicine using following key words and Boolean operators: transplantation AND

classification, transplantation AND oral manifestation, transplantation AND dental management, transplantation AND drug, transplantation immunology, pre transplantation AND post transplantation dental care.

The primary emphasis of the search was on systemic reviews and meta-analysis of various dental management strategies for transplant patients. Four reviewers contributed in reviewing and abstracting data from the literature and about 82 papers were independently reviewed by a primary reviewer out of which only 50 articles were finally selected for the review based on their relevance.

The result of this review was obtained after selecting eight articles on transplant immunology, fourteen articles pertaining to oral manifestation and twelve articles on each pretransplantation and post transplantation separately and one article combined to the dental management of transplant patients. Dental implication due to various drugs was done referring to four articles distinctly and five articles in combination with other subtitles of the article.

Classification

Transplantation has been can be classified and sub classified by various authors based on clinical type and also genetic relationship of tissue (donor) to the recipient[3-5] (Table.1).

Table.1. Classification of Transplantations

Based on Clinical Type	Based on Source
Solia organ tissue	Autograft
Hematopoietic cell	Isograft
	Allograft
	Xenograft
	Umbilical cord

Transplantation Immunology

Antigen-presenting cells (APCs) are present virtually in all organs and in response to appropriate inflammatory stimuli mature APCs express major histocompatibility complex (MHC) class II, which is regulated by various cytokines such as interferon-γ and tumor necrosis factor. Specific immune response is expressed by the allogenic graft, which can activate

particularly recipient's T lymphocytes either directly or indirectly [3,6,7]. In the direct pathway, recipient's T lymphocytes recognize native MHC molecules expressed on graft-associated APCs. In the indirect pathway, recipient's T lymphocytes recognize donor alloantigen derived peptides in the self MHC molecules expressed on recipient APCs[7].

Activated T helper cells further produce certain lymphokines and cytokines that promote the activation of cytotoxic T cells, B cell, natural killercell and macrophage activity. These further mounts into various immune reactions, leading into direct tissue damage and ultimately graft rejection[3,8-10].

Graft rejection may be acute manifesting within days to weeks or hyper acute occurring within minutes to hours into immediate organ failure or chronic which is slow and insidious seen within months to years and resulting into gradual organ failure[3]. Direct pathway pre dominates in early post-transplant and is a major factor in acute rejection whereas indirect pathway may be important in sustaining an ongoing, persistent response. Immunosuppressant are utilised and modified lifelong, mainly to prevent graft rejection and also to preserve the patient's immunity with the least possible alteration[6,11-13].

Oral Manifestation

Common oral infections like dentoalveolar abscess, gingivitis and periodontitis may exhibit in severe forms and are also of great concern because of its probability of ending into a fatal systemic infection in these immunocompromised patients[3]. Infective endocarditis in heart transplant patients, bacteremia and septicaemia have been reported but none have been due to oral source of infection[12].

Recurrent herpes simplex due to Herpes Simplex Virus, oral hairy leukoplakia due to Ebstein-BarrVirus and CytomegaloVirus infections has been observed in its severe form and with delayed healing[12,14,15]. According to a literature published in 2009, 80% of the invasive fungal infections are due to Aspergillus and Candida which classically occur within the first month after transplantation[16]. Oral candidiasis and Candidaemia are the most common clinical manifestation of invasive candidiasis, and liver transplant recipients have the highest reported incidence of Candida infection.

Cyclosporine induced gingival enlargements are manifested leading into plaque accumulation and further deterioration of periodontal tissues. Gum hypertrophy starts at 1-3 month after

the initiation of the immunosuppressive treatment, at the interdental papillae and then affects marginal and papillary tissues. Sometimes the papillary lesions in the gingiva show large cauliflower like growth, causing difficulty in mastication, speech and causing aesthetic hinderenceshindrances . It was noticed that male patients were more affected, and the symptoms were more severe in young patients[17,18-21]. This can be minimised by switching over to newer generation of immunosuppressive agents that do not cause gingival hyperplasia[12,22].

Salivary gland dysfunction is commonly seen in patients who have undergone radiotherapy or chemotherapeutic preconditioning regimen. Oral mucositis is another painful debilitating condition seen in haematopoietic stem cell transplantation (HSCT) patients with preconditioning regimens like whole body radiation, chemotherapy or both prior to transplant in order to completely eradicate the disease and to suppress the immune reactions[3,23]. Especially in children with solid organ transplant, the prevalence of oral mucosal disease and gingival enlargement was low, but the prevalence of caries rate was high which should be best managed by preventive dental care and at the earliest by appropriate restorative method[24].

Graft versus host disease (GVHD) may be acute or chronic occurring within or after 100 days respectively and may manifest in mouth, gastrointestine, skin and/or liver. Oral GVHD is usually associated with xerostomia, sensitivity to acidic or spicy food and increasing tenderness inferred to be due to lymphocytic infiltration of salivary tissue[17,25].

In a prospective study of 60 long-term survivors following allogeneic BMT, oral atrophy, erythema, and lichenoid lesions of the buccal and labial mucosa were significantly associated with development of chronic GVHD[26]. Lichenoid reactions manifestion varies from fine white reticular striae on buccal surfaces to large plaques on the buccal surface or the lateral tongue[26]. These patients are more prone to develop neoplasms like lymphomas, Kaposis sarcoma and squamous cell carcinoma, but those liver transplant recipients with history of tobacco and alcohol abuse have increased risk of oral cancer[12,27].

Dental Management

Dental management of transplant patients begins with meticulous screening and planning prior to the transplantation. Unless the patient is critically ill and has significant end organ

disorders, consideration to pre transplantation dental treatment is given, especially in HCT because of the severe immunosuppression likely to occur[3].

Pre-Transplantation Dental Care

The pre transplantation screening examination should consist of detailed medical history of associated end organ disease, thorough extraoral, intraoral examination and precise radiographic study with appropriate laboratory evaluation.

Renal disorders may contribute to hypertension and also have defective drug metabolism. Changes into suitable drugs and their dosages should be done depending on the severity of the end stage disease[28,29]. Those suffering from end stage liver disorders are prone for excessive bleeding and their drug metabolism is also hampered. Therefore, dosing amounts and/or frequency should be altered depending upon the shunting of blood away from the liver, decreased protein formation, altered or delayed drug metabolism, increased susceptibility to the metabolized drug's intermediate compounds, and drug interactions[30,31]. Patients with severe coronary artery disease or congestive cardiac failure are not able to withstand the stress of elective dental treatment prior to transplantation.

Additionally, they may be on anticoagulants which increase the risk of bleeding. Candidates for lung transplantation are on oxygen therapy and elective dental treatment should be postponed unless emergency, where it should be performed with the use of combustible sources[3]. Pancreatic transplant candidates are poor wound healers with defective glucose metabolism and prone for insulin shock. Prior to dental treatment consideration to glucose level, coagulation complication and drug metabolism should be given[3]. All potential sources of oral infection should be eliminated by dental treatment in hematopoietic stem cell transplant candidates before thepreconditioning to avoid complications like infections, increased bleeding due to pancytopenia[3,5].

Based on the literature review determining the medical risk benefit ratio in pre transplantation period, the most definitive treatment plan in pretransplantation period proposed should be given (Table.2).

All the elective treatments must be carried under antibiotic prophylaxis as per the American Heart Association [AHA] recommendation[34]. Clindamycin and erythromycin can be safely given in kidney disorders and in case of liver disorders penicillin, amoxicillin, cephalexin can

be given without any dose change[17,29]. Patients prone for excess bleeding due to anticoagulants should be consulted with their physician and the levels can be altered. Those with liver disorders may need dental treatment in a hospital setting with vitamin K and clotting factors under physician consultation[35].

Acetaminophen can be safely given in renal diseases, but it should be carefully given in minimal doses to adults in divided doses of no more than 4 gram per day for 2 weeks without adverse hepatic effects[12]. Patients should be strongly advised not to take alcohol during the period when they are using acetaminophen. Lidocaine within normal limits can be safely used in both kidney and liver failures[36].

Table.2. Pre Transplantation Dental Care: General guidelines[3,5,12,24,32,33]

Patient's physician consultation and medical status and drug intake evaluation
Oral hygiene and home care instruction with fluoridated and antiseptic mouthwashes
Oral Screening with clinical examination and radiographic survey
Supragingival and subgingival calculus - oral prophylaxis *#
Dental caries – appropriate Restoration#
Pulpitis – Pulpectomy or RCT#
Periapical pathology – RCT#
Periodontal pathology
Mild to moderate – oral prophylaxis *
Severe –extraction *#
Endo perio lesions with poor prognosis – extraction*#
Symptomatic partially erupted third molar- extraction*#
Denture corrections

* Precaution in liver and bone marrow disorder patient due to excess bleeding

Precaution in cardiac disorder patients who cannot withstand any stress and are on anticoagulants

Post Transplantation Period

Post transplantation period can be categorised as immediate post transplantation period, stable post transplantation period and chronic rejection period[3,12,35]. Elective dental treatment not carried in pre transplantation period due to risk associated with end organ disease should be planned in the stable period when the transplant is properly functioning in the body.

Immediate post transplantation period varies from 1-3 months, wherein the transplant is susceptible for rejection due to severe immunosuppression. Elective dental treatment is

postponed except in the case of infections wherein emergency care is provided under the consultation of transplantphysician[37].

The oral ulcer in these patients should be treated promptly and definitively as it can be a source of fatal systemic infection. In an episode of infection, an adequate empirical therapy administered within 24 hours of the culture collection time was found to be more appropriate[38,39]. Invasive candidiasis is prevented by targeted prophylaxis therapy wherein subgroup of recipients determined to be high risk as defined by clinical, laboratory or epidemiological characteristics are treated. Infectious disease Society of America guidelines recommend targeted prophylaxis with flucanozole 200-400 mg daily (3-6mg/kg) or liposomal amphotericin B (1-2mg/kg) daily for at least 7-14 days[16,40].

Effective treatment of established fungal infection needs early diagnosis, aggressive debridement when possible, fungicidal therapy and reduction of immune suppression. Amphotericin B deoxycholatehas been considered as the gold standard for therapy, but its administration is often associated with renal toxicity and infusion-related side effects[40].

Xerostomia should be managed by various salivary substitutes and sialogogues like cevimeline and pilocarpine. Literature review shows that further, 1.1% neutral sodium fluoride toothpaste, 0.63% stannous fluoride rinse or 0.4% stannous fluoride should be prescribed to prevent the occurrence of root caries[41-43]. Emphasis to maintain good oral hygiene is given, with proper home care instructions and antiseptic mouth washes as even the contaminated saliva can lead into various infection.

Stable post transplantation period is the ideal time for any elective dental treatment as the patient is medically stable. However, it should be done under transplant physician consultation with empiric antibiotic therapy assessing the risk of immunosuppression and drug interaction. Corticosteroid supplementation should be adequately given depending on the dental procedure to avoid adrenal crisis[44-46].

Dental Implication due to Medication

The antibiotics frequently used for dento-alveolar infection, can cause interaction and alter the gastrointestinal flora and thus increase the drug levels of the immunosuppressant. Nonsteroidal anti-inflammatory agents may also potentiate the nephrotoxic effects of cyclosporine and tacrolimus[47]. Antacids (containing magnesium or aluminium) and bile acid

binders also interfere with the absorption of the immunosuppressant. Considering all these factors adequate drugs should be prescribed in association with the transplant physician.

Dental Implication due to Immunosuppression

Infection and risk of cancer are the two complications induced due to immunosuppression. The immunosuppressive agents may cause major side effects in the oral cavity like gingival enlargement, gingivitis, glossitis, xerostomia, halitosis, abnormal taste, esophagitis, oral ulcerations, stomatitis, anemia, fungal and viral infections[26,48]. It can also lead to development of "de novo" malignancies in the oro-maxilo-facial area, such as: epithelial dysplasia, squamous oral carcinoma, basal cell carcinoma, Kaposi's sarcoma. The incidence of "de novo" malignancies increases proportionally to the time period since the transplantion, from a rate of incidence of 10% after 10 years, to 40% after 20 years after the transplant[17,18,27,49].

HCT patients are more prone for immunosuppression and infection than solid organ transplant recipients, because of prior conditioning with intensive chemotherapy and/or radiotherapy to kill residual malignant cell and to prevent rejection. Therefore appropriate prophylactic antibiotics should be given as per the AHA recommendations for prevention of infective endocarditis[34,50]. Regular follow ups should be done for early detection and treatment of cancer. Chronic rejection period starts when a grafted organ begins to fail and dental care is complicated because of the risk associated with organ failure and severe immunosuppression. Only emergency care should be provided in association with the transplant physician in a hospital setting.

Conclusion

Quality of life of transplant recipients should not be impaired due to improper dental care. Literature review shows that Ppre transplantation dental care should be emphasised and all the potential dental needs should be modified and met as per the medical status of the patient. In the post transplantation period routine dental check-up, radiographic screening should be encouraged to eliminate any potential sources of infection and all the elective dental treatment should be provided in the stable period under transplant physician consultation. According to few studies any minimal source of infection should be therapeutically managed at the earliest with appropriate drugs which do not cause any interference in the metabolism.

Further, patient should be educated about the importance of updated medical status because of the transitionary phases in post transplantation period. Nevertheless, most of the authors have unanimous opinion that oral hygiene and home care instruction with regular topical fluoride applications and antiseptic mouthwashes plays a key role in improving the dental health of the patient.

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