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Auto-Transplantation of Wisdom Tooth Buds and Other Possible Uses of Them to Replace Missing Teeth

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Abstract

Vestigial organs, including wisdom teeth, are remnants of evolutionary development no longer necessary for modern humans. However, wisdom teeth frequently cause issues such as pain, infection, and impaction. This study explores the innovative use of third molar tooth buds, particularly for young patients either who lose their first or second molars early, could be due to extraction as apart of treatment. By extracting these tooth buds at the late bell stage (8-10 years old) and auto-transplanting them into extraction sockets, supported by biocompatible scaffolds and drug delivery systems combined with cell homing techniques, a cost-effective and efficient alternative to traditional dental implants and stem cell-based tooth regeneration is proposed. This method leverages the natural developmental process of the tooth bud, significantly reducing the complexity and expense associated with dental restoration, while also promising quicker recovery and biointegration compared to existing methods.

Keywords: Vestigial organs, Extraction sockets, Impaction, Consolidate, Molars

Introduction

The third molars or wisdom teeth, in humans begin developing around the age of six and reach the late bell stage between eight and ten, erupting into the oral cavity by 17-21yrs of age [1]. Wisdom teeth, a common vestigial organ, can lead to complications such as pain, infection, impaction, pericoronitis, and difficulties in eating and jaw movement, affecting a large portion of the population[2].

This study explores the potential of using these third molar tooth buds for a number of ways, including autotransplantation into extraction sockets, particularly for young individuals who have got their permanent first or second molars extracted. The proposed method involves extracting the developing tooth bud at its late bell stage and transplanting it into the extraction socket using biocompatible scaffolds and drug delivery systems, along with cell homing techniques to facilitate regeneration.[3,4,5]

Recent advancements have shown successful tooth bud regeneration in animal models, such as rabbits, indicating a promising scope for further research.[6,7,8]. While developing an entire tooth from pluripotent stem cells is a significant area of study, it is time-consuming and requires extensive tissue engineering[3]. In contrast, auto-transplanting a developing tooth bud into an extraction socket can achieve complete tooth formation in a relatively shorter time with minimal specialised tissue engineering requirements.

This method not only offers a quicker and more straightforward solution but also proves to be more cost-effective compared to traditional tooth replacement methods and whole tooth regeneration from stem cells. Once developed, this approach could provide a viable alternative for dental restoration, especially for young patients needing early molar extractions. The aim of this review is to consolidate existing research and methodologies to assess the feasibility and potential benefits of wisdom tooth bud autotransplantation in humans, paving the way for innovative and practical dental regenerative therapies.

There are other valuable uses with the extracted 3rd molar tooth buds which are discussed in this study

Material methodology

To review the literature, Studies were selected from PubMed, Scopus, Web of Science, and Google Scholar without restrictions on publication year, to provide a comprehensive overview of current knowledge on 3rd molar tooth bud autotransplantation relevant to the future scope of practice implementation. The review focused on the entire process right from the wisdom tooth bud extraction from the alveolar bone till its implementation into the extraction socket including other possible uses of the extracted tooth buds. The search terms included: “Wisdom tooth buds,” “Tooth bud extraction,” “3rd molars,” “tooth bud transplantation,” “Biomaterial scaffold,” “Growth factors ,” “Cell homing,” “Decellularised tooth bud,” “Subnormothermic temperature,” “Cryopreservation” and “Allotransplantation.” The research encompassed, Case reports, laboratory studies, clinical studies, and systematic reviews

The 3rd molars

The wisdom teeth are considered as vestigial organ. Vestigial organs are those that were functional in ancestors but are useless now due to evolutionary changes. Apart from being useless, these teeth cause serious problems like impaction, TMJ problems, crowding, ectopic eruptions and more. Nearly 65-72% of Americans face difficulty with at least 1 of their wisdom teeth[2]. Nearly 35% patients are having at least one of their wisdom teeth missing and 90% of them having impacted 3rd molars[9]. Majority of these problems are solved by extraction of these 3rd molars after the patient starts to suffer. But this article discusses about other alternatives for the conventional methods. It explains as,

If the 3rd molars are extracted from the dental arch even before they erupt into the oral cavity, there are a number of prospective outcomes and they are listed as follows:

- They can be used to autotransplant into immediately extracted alveolar sockets replacing the missing teeth
- They can either be donated for other patients for allotransplantation

- They can also be used as decellularised tooth buds for future study or as a scaffold for a stem-cell based whole tooth regeneration
- Can also be stored in appropriate conditions for future use.

The advantages of these methods will be discussed in this article.

3rd molar tooth bud extraction

The tooth development occurs in various stages viz bud, cap, bell, appositional and mineralisation, among which the crown structure is defined from the cap stage and calcification occur during the mineralization phase of tooth development[1]. Hence the appropriate time for extracting the bud depends on the future requirements[6,10]. They are listed as follows:

If the tooth bud is used for immediate transplantation:

- The bud could be used to replace the missing molar of any arch in the same or a different individual if extracted before the root formation starts, as it would not facilitate the development in the opposite arch as the root anatomy differs[6].
- If the tooth to be replaced is in the same arch then the 3rd molar tooth germ can be extracted even after the root formation is started[8].
- It is also possible to implant the developing tooth bud in the extraction socket of other teeth like anteriors or premolars of same or a different individual when extracted in the bud or cap stage of development depending on the case[10].
- The tooth germs can be used for scaffolds or preserved for future use if extracted in the bud stage of development[8].

Tooth bud transplantation

There were few successful experiments done on animals like mice, rabbits, tigers and also humans where the tooth buds were transplanted and the outcomes were promising for future hope[6,7,11,12,13,14,15]. But there were few problems like the insufficient enamel, lack of nerve innervation, short roots and impaired PDL development[11]. The causes for these problems are due to the damage caused to the tooth bud are either during implantation or improper placement or implantation of bioengineered tooth-buds, insufficient nutrient supply for the tooth-bud after implantation.

These problems can be cleared if the following protocol is followed

After the tooth bud is extracted, in all the previous experiments, the tooth buds were directly implanted into the extraction sockets, because of which, the bud when implanted into bony socket providing indefinite place for the cell attachment and lack of casing for the bud causes damage to the cells of the bud, instead if the tooth buds are first placed in a scaffold made of biomaterial, these problems could be checked[3,4,16,17,]

Biomaterial Scaffold

A scaffold is a framework that supports a construction, similarly such framework made with synthetic or natural biomaterials like a hybrid of poly-ε-caprolactone (PCL) and hydroxyapatite (HA) provides support for implanting proliferative stem cells.[3]

The main advantages of these biomaterial scaffolds is that it forms a casing framework that protects the developing tooth bud when implanted into the extraction socket from damage since every cell in a tooth bud is proliferative for the whole tooth development hence should be protected[4].

They can be designed in the shape of the required tooth design by 3D printing, this helps to obtain the necessary shape of the tooth to be replaced within the socket so that the proliferating cells and their apposition can be obtained in the desired shape[16].

Apart from protection, site for cellular attachment and designing the shape of tooth, the other major function of a scaffold is drug delivery system. The framework used in a scaffold provides fine drug delivery system that can be used to deliver either growth factors or cell homing substances to nourish the developing bud and provide required factors for the differentiated growth of all tissues of tooth [17].

Application of growth factors to the implanted tooth bud for cell homing effect:

What are growth factors?

Growth factors are polypeptides or proteins that bind to specific receptors on the surface of target cells, modulating cellular activities such as migration, proliferation, differentiation, and apoptosis. They act as signalling molecules that mediate intracellular communication, often functioning locally in an autocrine or paracrine manner[4,5].

What is cell homing?

Cell homing refers to the process of guiding host endogenous cells to the site of dental pulp–dentin regeneration by delivering growth factors instead of directly transplanting cells. This approach leverages the body's natural mechanisms to attract stem/progenitor cells to the area where regeneration is needed, thereby promoting the formation of new dental pulp-like tissue and dentin. This method relies on growth factors to orchestrate the migration, proliferation, and differentiation of these cells to restore the vitality and function of the pulp-dentin complex [4,5,16]

How do they help in cell proliferation?

Growth factors initiate intracellular signalling cascades by binding to cell surface receptors. This signalling can stimulate cellular activities such as DNA synthesis, cell division, and survival, thereby promoting cell proliferation [18,19].

Mechanism of action of growth factors on proliferative cells

These are few growth factor that have shown positive outcomes in recent experiments by binds to specific receptors on proliferative cells, initiating signalling pathways that regulate various cellular processes:

- PDGF: Promotes angiogenesis and cell proliferation by binding to PDGFR receptors.
- TGFβ: Involves in cell differentiation and proliferation through TGFβ receptors.
- BMPs: Induce osteogenesis and chondrogenesis via BMP receptors.
- VEGF: Stimulates angiogenesis by interacting with VEGF receptors.
- FGF: Facilitates cell migration, proliferation, and differentiation through FGFR receptors.
- IGF: Contributes to cell proliferation and differentiation via IGF-1R receptors.
- NGF: Supports neuron survival and differentiation through TrkA receptors.
- SDF-1: Attracts stem cells to the injury site by binding to CXCR4 receptors.

These growth factors can be administered to the proliferating tooth bud through 3D scaffold prepared in the shape of the desired tooth to be replaced

The delivery of growth factors can successfully orchestrate the regeneration of dental pulp-like tissue and dentin in vivo by attracting and stimulating the proliferation and differentiation of stem/progenitor cells, leading to the restoration of the pulp-dentin complex, bone and PDL within the scaffold. This cell-homing approach presents a viable alternative to traditional cell transplantation methods [4,5,16,19].

Decellularized tooth bud scaffolds

1. What are decellularized tooth bud scaffolds?

- Decellularized tooth bud scaffolds (dTBs) are natural tooth bud tissues from which all cellular components have been removed, leaving behind the extracellular matrix (ECM). This ECM retains the natural biochemical and structural framework necessary to support the growth and differentiation of new cells into functional tooth tissues[17].

2. How are they used for whole tooth regeneration?

- Decellularized tooth bud scaffolds are recellularized by seeding them with specific cell types, such as dental epithelial cells, human dental pulp cells, and endothelial cells. These cells attach to the scaffold, proliferate, and differentiate into the various cell types required for tooth formation. The recellularized dTBs are then implanted into the jawbone, where they integrate with the host tissue, forming organised structures like dentin, enamel-like tissues, and pulp, eventually leading to the regeneration of a whole tooth[12,16,17,20].

3. How are they better than 3D-printed scaffolds?

- Decellularized tooth bud scaffolds are superior to 3D-printed scaffolds because they retain the natural ECM's intricate biochemical and structural cues, which are crucial for proper cell attachment, differentiation, and tissue organisation. This natural matrix provides an optimal environment that closely mimics the native tooth development conditions, enhancing the efficiency and success of the regeneration process. In contrast, 3D-printed scaffolds, although customisable, often lack the precise biological complexity and functional cues present in natural ECM, which can limit their effectiveness in promoting full tissue regeneration.

Preserving the extracted tooth bud

Subnormothermic temperature refers to a temperature that is lower than normal body temperature but still above freezing. In this study, they specifically used a subnormothermic temperature of 25°C (77°F) for preserving tooth buds.

Subnormothermic temperature:[21]

- Used to preserve tooth buds for extended periods (up to 28 days in the study).
- May be better for preserving stem cells in the tooth bud based on gene expression observed in the study.
- Simpler to implement as it doesn't require specialised equipment for freezing like cryopreservation.
- Might not work for long-term storage (beyond a month) as observed in the study.

Cryopreservation:[7]

- Typically involves freezing tissues to very low temperatures (-80°C or lower).
- Can preserve tissues for much longer durations than subnormothermic temperatures.
- Complex process requiring specialised equipment and cryoprotectants to prevent ice crystal formation.
- May damage tissues during the freezing and thawing process.

subnormothermic temperature might be a more suitable method for tooth bud preservation for a short term.

The medium used to preserve tooth buds can be few like: Dulbecco's modified Eagle's medium (DMEM)/F-12 supplemented with fetal bovine serum (FBS), ascorbic acid, L-glutamine, and penicillin/streptomycin. These have shown promising outcomes in regenerating the tooth buds after preservation[7,21].

Challenges for the method of tooth regeneration using other methods

- Short roots and insufficient enamel formed in the generated tooth compared to normal teeth due to damage caused to the tooth bud cells while implanting

- Impaired PDL and Bone formation due to lack of proper supporting factors from the host region[22,23]
- Lack of nerve innervation into the Transplant as an erupted or completely mineralised tooth with closed apices doesn't have enough space at the root apex for nerve and vasculature to innervate.
- Whole tooth regeneration using stem cells takes very long time and till now developing individual tooth tissues like dentin, enamel, cementum, PDL was thought to be more fruitful.
- Graft rejection due to decellularized teeth scaffolds from animals
- Implants are not suitable for young adolescents and patients with other problems

Modifications to overcome those challenges

- Use of scaffolds to implant the Tooth bud into the extraction socket.
- Administering growth factors and cell homing mechanism.
- Transplanting a tooth bud or tooth with open apex.
- An already formed tooth bud have all the-necessary progenitor cells that form the tooth tissues and has a potential of developing into a complete tooth naturally.
- Donation of tooth-buds of 3rd molars for allotransplantation to reduce the effects of graft rejections. As there are nearly 158 million people who are edentate and are in need for their substitution[17,24,25].
- Auto-transplanting or allotransplantation of 3rd molar tooth buds would be more suitable for patients for whom implants are not compatible.
- suitable for patients for whom implants are not compatible.

Advantages

- **Cost-Effective Alternative**: This method presents a cost-effective solution compared to traditional dental implants and stem cell-based tooth regeneration, making it more accessible to a broader population.
- **Reduced Complexity**: Leveraging the natural developmental process of the tooth bud minimises the need for extensive tissue engineering, simplifying the procedure[22].
- **Quicker Recovery**: Patients can experience quicker recovery and biointegration compared to existing methods, reducing downtime and enhancing overall patient satisfaction.
- **Minimally Invasive**: The approach reduces the invasiveness of the procedure, as it involves natural tooth development rather than synthetic implants or extensive tissue engineering[23].
- **Natural Tooth Development**: Utilising the natural developmental potential of the tooth bud ensures a more biologically integrated and natural tooth formation process.
- **Versatile Applications**: The method is applicable for autotransplantation, allotransplantation, and preservation for future use, offering multiple solutions for dental restoration.
- **Enhanced Biointegration**: The use of biocompatible scaffolds and drug delivery systems promotes better integration of the transplanted tooth bud with the surrounding tissues.
- **Reduced Need for Implants**: This approach provides an alternative for patients who may not be suitable candidates for traditional dental implants, such as young adolescents.
- **Potential for Donation**: Third molar tooth buds can be donated for allotransplantation, addressing the

needs of a larger population and reducing the impact of graft rejections

Disadvantages

- **Technical Challenges**: Extracting and transplanting tooth buds at the optimal developmental stage requires precise technique and expertise, potentially limiting widespread adoption.
- **Limited Long-Term Data**: There is a lack of long-term clinical data on the success and durability of this method, making it difficult to fully assess its efficacy and safety over time[25].
- **Specialised Equipment Needed**: The use of biocompatible scaffolds, drug delivery systems, and preservation methods requires specialised equipment and materials, which may not be readily available in all dental practices.
- **Potential Ethical Concerns**: The use of tooth buds for transplantation, especially in allotransplantation, could raise ethical concerns regarding consent and the use of biological materials[24].
- **Dependency on Donor Availability**: The success of allotransplantation depends on the availability of suitable donors, which could limit the applicability of this method in certain regions or populations.

Conclusion

The innovative approach of utilising wisdom tooth buds for auto-transplantation into extraction sockets presents a promising advancement in dental regenerative therapies. By extracting tooth buds at the late bell stage and leveraging biocompatible scaffolds combined with drug delivery systems and cell homing techniques, this method provides a cost-effective and efficient alternative to traditional dental implants and stem cell-based tooth regeneration. This process reduces complexity and expenses while ensuring quicker recovery and integration compared to existing methods. Furthermore, the natural developmental potential of the tooth bud minimises the need for extensive tissue engineering, offering a straightforward solution for young patients requiring early molar extractions. This technique not only holds the potential to revolutionise dental restoration but also addresses the limitations of current methods, such as insufficient enamel, impaired periodontal ligament development, and nerve innervation issues. Overall, the transplantation of third molar tooth buds represents a significant step forward in the field of dental regeneration, combining simplicity, efficiency, and cost-effectiveness to meet the needs of patients and practitioners alike.

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