Adverse Effects of Orthodontic Aligners & Possible Mechanisms - A Review

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Abstract

There has been a rising trend in the number of patients seeking orthodontic care, especially among the adults. This drift towards adult orthodontics indicates increased social awareness among the general population about their esthetics. Further, this phenomenon has additionally been supported by the use of orthodontic aligners as they are esthetically superior choice for adult orthodontics which requires mild to moderate correction. Orthodontic aligners are made up of various thermoplastic materials e.g. Bioplast, Copyplast, Duran, Hardcast, Imprelon, Essix A+, Essix C+ and Invisalign.. Orthodontic aligners, namely Invisalign and others are associated with adverse effects which diverge from a local response to various types of systemic manifestations. In this article the adverse effects associated with aligners and their possible mechanisms are reviewed. The databases Google Scholar, Medline/OvidSP, Web-of-Science and BIOSIS search engines were searched. The search criteria used was adverse/ harmful/ deleterious effects of sequential aligners/ clear aligners/ aligners/ Invisalign system. The articles which laid emphasis on adverse effects of aligners and the possible mechanisms for such reactions were included. Some of the adverse effects include difficulty breathing, sore throat, swollen tongue, hives and itchiness, anaphylaxis, chest pain, cough, nausea, difficulty swallowing, blisters on tongue. The possible mechanisms for these adverse events are attributed to the composition/ products released by Invisalign/ sequential aligners, namely, Bisphenol A and polyurethane. The potential mechanism is due to the presence of isocyanates in polyurethane, which bind with proteins and other biomolecules forming haptens. These can sensitize the immune system leading to potential allergic responses.

Keywords: Orthodontic aligner, Adverse affects, Mechanism of Action, Adult orthodontics, Invisalign/sequential, Thermoplastic materials.

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Introduction

Sequential aligners are excellent options for adults who are reluctant to wear fixed appliances and require mild to moderate corrections like space closure, alignment after interproximal reduction, dental expansion, flaring and distalization.[1,2] They are esthetically superior and also provide better plaque control.[3] However, aligners are not recommended to treat severe deep bites, anteroposterior corrections greater than 2mm, uprighting severely tipped teeth, or premolar extraction cases.[2] Furthermore, there is a paucity of studies that have examined the systemic adverse events associated with them.[4] This article reviews the adverse effects associated with the use of sequential aligners.

Historical Background

The number of people seeking orthodontic care has increased, with 5.9 million people seeking orthodontic care in United States alone. There has been a rise of 20% in the number of adult patients seeking orthodontic care.[4] This indicates increase in awareness about oral hygiene. which shall improve after orthodontic correction.[5] One of the primary motivating factors for adults who seek orthodontic care is the desire to improve their smile.[6]

Conventional orthodontic therapy involves the use of brackets and stainless steel wires. This fixed appliance therapy is associated with more favorable plaque retention sites which make maintenance of oral hygiene difficult, leading to detrimental effects on the periodontium.[7] Moreover, fixed appliance therapy is also associated with changes in color of the enamel. It occurs because of the irreversible penetration of the adhesive resins into enamel structure which is susceptible to both external and internal discoloration. [8]

Recently orthodontics has evolved with a more esthetic approach to reach the goals of orthodontic therapy. This involves the use of ceramic brackets, fixed lingual appliances and sequential aligners. Sequential aligners are usually worn for 24 hours a day and removed only while eating, drinking, brushing and flossing.[1] A new set of aligner is used after every 7-14 days till the desired tooth correction is achieved.[1,9] They are comfortable to wear and also cause less occlusal abrasion in people with parafunctional habits.[2]

Sequential aligners are made up of thermoplastic materials. Commonly used thermoplastic products along with their composition are shown in Table 1.[9] Thermoplastic appliances are also used as night guards, retainers and temporomandibular joint splints. Since they are used for months together in the oral cavity their biocompatibility is of utmost importance.[10]

Methodology

The databases Google Scholar, Medline/ OvidSP (includes EMBase), Web-of-Science and BIOSIS search engines were searched. The search criteria used was adverse/ harmful/ deleterious effects of sequential aligners/ clear aligners/ aligners/ Invisalign system. Further, the bibliographies of included publications and relevant articles for data that could not be found out by the above search strategy were also included.

The articles which laid emphasis on local and systemic effects of aligners and the possible mechanisms for such reactions were included. Inclusion was determined on reviewing the study abstracts alone, and certain articles which focused on the drawbacks/ limitations of aligners to treat certain type of malocclusions were rejected.

Adverse Effects of Aligners

Allareddy et al analyzed the adverse effects of the Invisaligns in particular, manufactured by the Align Technology. The Medical Device Reports (MDRs) were obtained from the Manufacturer and User Facility Device Experience (MAUDE) database of the United States Food and Drug Administration (FDA). The observation period was from November 1, 2006 to November 30, 2016 with a total of 173 MDRs reported. A total of 138 MDRs were reported by manufacturer (Align Technology) and 35 MDRs were reported voluntarily by either patients, family members of patients, or health professionals (including dentists, physicians, and other professionals).

26% (45) MDRs reports were serious or life threatening. There was a significant increase in the number of serious or life threatening MDRs reported during the year 2014-2016. 50% of the MDRs reported in the year 2014 and 46.7% of the MDRs reported in the year 2015 were categorized as serious or life threatening. The maximum number of MDRs were reported in the year 2011 (50 reports) and thereafter from 2012-2015 the trend of MDRs reported increased on a year to year basis.[4]

The adverse reactions reported varied from systemic manifestations like difficulty in breathing, hives and itchiness, anaphylaxis to local reactions like blisters or sores of lips, blisters or ulcerations on tongue, swelling of gums. Other events like lymph node enlargement, rashes on face or body, sinus tachycardia, palpitations, numbness of tongue, chest congestion, and joint pains were also reported but were less frequent. The patients believed that the reactions were reported after the use of Invisalign and the symptoms disappeared after discontinuation of the Invisalign.[4]

Awosika et al in their study described a case of angioedema, urticaria and stomatitis resulting from Invisalign use.[11] The adverse events associated with Invisalign use are briefly summarized in Table 2.

Similarly, Thavarajah and Thennukonda analysed the AER (Adverse Events and Reactions) associated with the use of sequential aligners from October 1, 2010 to September 30, 2015 collected from the MAUDE database.

This study reported a total number of 175 cases over a period of 5 years. The adverse effects reported were from 14 brands made by 6 manufacturers. One manufacturer had the

highest number of AERs (151). The maximum number of AERs were reported in the year 2011(59 events), followed by 29 events in 2015, 28 events in 2013, 27 events in 2014 and 24 events in 2012. [12]

The AERs were further categorized and grouped into (i) intraoral complications 68 (38.86%); (ii) Facial complication in the facial region 77 (44%); (iii) head and neck complication 96 (54.86%) ; (iv) head, neck, and dental complication 108 (61.71%) ; (v) head, neck, and oropharyngeal complications 132 (75.43%) ;(vi) head, neck, dental, and oropharyngeal complications 139 (79.43%).There were exclusive 20 (11.43%) dental complaints – four (2.3%) occlusion issues, three (1.7%) dental decay, five (2.9%) periodontal issues leading to loss of teeth and eight (4.6%) complaints of either unfavorable attrition, loss of veneers, and chipping of teeth. Limbs and generalized involvement such as rashes or hives were involved in 23 (13.14%) cases. Cases of nausea 12 (6.86%), gastrointestinal issues 11 (6.29%), neuromuscular issues 13 (7.43%), cough 13 s(7.43%), persistent headache 10 (5.71%), fever 3 (1.71%), cardiac issues 12 (6.86%) were also reported. Candidiasis, herpes infection, trigeminal neuralgia, ovarian cancer, gastrointestinal tumor, malignant melanoma, and liver damage, oral squamous cell carcinoma (OSCC) were also reported.[12](Table 3)

Discussion

The aligner's treatment demands are growing rapidly due to it being a better esthetic option than conventional braces. But as the saying goes "where there are roses there are thorns too" The studies mentioned show that the adverse effects due to the use of aligners include a localized response as well as systemic reactions like anaphylaxis. The probability of having an adverse effect involving lips, throat and dypsnea is high with the use of sequential aligners as compared to the general population.[12]

The adverse effects of aligners seem to be because of two potential components namely BPA(Bisphenol A) and polyurethane. Polycarbonate aligners are a potential candidate for BPA release. Molecules with double benzoic ring usually release BPA, and are known to have estrogenic action which mimics the female hormone estradiol. Various effects of BPA release include increased mammary gland tumors, precancerous lesions in prostates of neonatally exposed animals, development of hyperglycemia and insulin tolerance, elevation of reactive oxygen species, and oxidative stress.[13]

Elidaes et al investigated the cytotoxic and estrogenic action of aligners' in-vitro using an in-vitro protocol and assay. The effects of proliferation in the presence of the Invisalign appliance eluents on the estrogen sensitive and insensitive cell lines were studied. It was found that the eluents from the aligners have no effects on cell proliferation on all the concentrations studied.[13]

The other potential component is polyurethane and is the basic polymeric constituent of Invisalign aligners.[13] Polyurethane is not an inert material but it is affected by heat, moisture and enzymes.[14] It is a product of 4,4 methylene diphenyl diisocyanate and 1,6 hexanediol precursors.[9] Isocyanates bind with proteins and other biomolecules when they come in contact with tissue, forming haptens. These can sensitize the immune system. Moreover, death of / damage to epithelial cells or loss of integrity of epithelium can lead to isocyanate conjugated protein exposure to the immune system leading to sensitization.[9]

Premaraj et al showed the effect on keratinocytes on contact with Invisalign eluate in vitro. Keratinocytes were exposed to saliva-solution eluate and saline-solution eluate. Cells showed changes in micromotion when treated with saline-solution eluate. This indirectly indicates cytotoxicity. Moreover, there was increased cell permeability on exposure to the saline-solution elaute, whereas barrier function was increased and cell permeability decreased on exposure to saliva-solution eluate. Saline-solution eluate exposure also showed a decrease in optical density, this indicates decreased metabolic activity / cell death.[9]

Isocyanates are responsible for contact allergic reactions and have known to cause allergic reactions which involve gingival mucosa and also have systemic manifestations like respiratory difficulties.[14,15] Also, it is reported that Invisalign use in-vitro led to increased cell death, compromised membrane integrity and reduced cell-to-cell contact and mobility, which may lead to isocyanate allergy.[4,13] The probable mechanisms of action along with their potential effects are briefly summarized in Table 4.

Schutter et al studied significant changes after in vivo exposure of aligners which included cracking, wear of contact points, adsorption of proteinaceous material, and regional calcification of central fissures. However, in-vitro studies demonstrated that no traceable amount of substances in an ethanol aging solution was found to leach from the Invisalign appliance.[16]

The adverse effects associated with the use of aligners have an immunologic response associated with the use of aligners and the effects are potentially because of diisocyanates use.

Conclusion

All these studies show that aligners are associated with certain adverse effects and further studies are needed to investigate the potential effects of aligner use. There is a need for increased awareness among dental/ orthodontic professionals offering aligners treatment, regarding the potential adverse effects of aligners. Further it is necessary that the patients opting for aligner treatment should also give the informed consent for possible adverse effects and an advisory should also be issued by aligners companies on their product packaging meant for patients. Although the adverse effects of aligners are too little compared to its benefits but nevertheless "the well build clinical reputation can be destroyed by a single failure".

Table 1. Commonly used thermoplastic products along with their composition is shown[9]

Thermoplastic Product	Composition
BIOPLAST	Ethylene-vinyl acetate copolymer
COPYPLAST	Polyethylene
DURAN	Polyethylene terephthalate glycol
HARDCAST	Polypropylene
IMPRELON	Polycarbonate
ESSIX A +	Copolyester
ESSIX C +	Polypropylene / ethylene copolymer (>95%), stabilizers (<5%)
INVISALIGN	Polyurethane from methylene diphenyl diisocyanate and 1,6-hexanedial, Additives

Table 2. Adverse effects of Invisaligns

Type of Aligner	Total Number of Cases / Time	Adverse Events		Mechanism of Action	Reference
		Type of Clinical Adverse Event	Number of Cases		
Invisalign (Align technology)	173 (From November 1, 2006 to November 30, 2016)	Difficulty breathing	56	Not mentioned	Allareddy et al
		Sore throat	35		
		Swollen throat	34		
		Hives and itchiness	31		
		Anaphylaxis	30		
		Swollen Lips	27		
		Laryngospasm	24		
		Chest pain	19		
		Cough	19		
		Nausea	18		
		Difficulty swallowing	12		
		Dry mouth	11		
		Headache	10		
		Swelling of eyes	9		
		Blisters of lips	9		
		Fatigue	8		
		Burning / tingling / sore tongue	7		
		Blisters on tongue	6		
		Swelling of gums	4		
Invisalign	1 (time not specified)	Angioedema urticaria and stomatitis	1	The reaction was similar to sensitivity to isocyanates; a component of Invisaligns	Awosika et al

Table 3. Adverse effects of sequential aligners

Type of Aligner	Total Number of Cases / Time	Adverse Events		Mechanism of Action	Reference
		Type of Clinical Adverse Event	Number of Cases		
Sequential aligners	175 (October 1, 2010 to September 30, 2015)	Dyspnea	54	Not mentioned	Thavarajah and Thennukonda
		Abnormalities of throat	66		
		Abnormalities of tongue	38		
		Abnormalities of gingival	22		
		Abnormalities of palate	52		
		Abnormalities of lips	39		
		Abnormalities of face	20		
		Abnormalities of cheek	11		
		Mouth ulcers	11		
		Distant sites	23		

Table 4. Probable mechanisms for adverse effects due to Invisalign

MATERIAL	METHOD USED	MECHANISM OF ACTION	RESULT	REFERENCE
Invisalign	Cytotoxicity assay: Cells were plated in a medium containing 10% FBS* for 18 hours The aligner immersion media was added. After 48 hours of incubation, the medium was replaced with MTT† in serum-free, phenol-red-free DMEM‡ for further 4-hour incubation. Then, the MTT formazan was solubilized in isopropanol, and the optical density measured.	Release of bisphenol A (BPA) from double benzoic acid ring present in the aligners. BPA is known for its estrogenic actions as it mimics the action of female hormone estradiol	No cytotoxic or estrogenic action was induced by the aligner eluents	Elidaes et al
	Estrogenecity assay: In this assay the cells were plated in mirco-wells and further exposed to two cell lines an estrogensensitive(MCF§-7) and an estrogen-insensitive (MDA-MB‖).			
Invisalign	Oral epithelial cells were exposed to eluate obtained by soaking Invisalign plastic in either saline solution or artificial saliva for 2, 4, and 8 weeks.	Isocyanates bind with proteins and other biomolecules when they come in contact with tissue, forming haptens. These can sensitize the immune system causing allergic reactions	Increased cell death, compromised membrane integrity and reduced cell-to-cell contact and mobility, which may lead to allergy.	Premaraj et al

* FBS (fetal bovine serum)
† MTT ((3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide)
‡ DMEM (Dulbecco's Minimal Essential Medium)
§ MCF (Michigan Cancer Foundation)
‖ MDA-MB (M.D. Anderson and MetastasisBreast cancer).

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