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Assessment of In-Vivo Toxicity of Light-Cure Resin Veneer Luting Cements Using a Zebrafish Model

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ABSTRACT

Objective: This study aimed to assess the cytotoxic effects of two resin-based veneer luting cements, Calibra veneer and Variolink, using an in-vivo zebrafish model. The null hypothesis tested was that these cements would not induce cytotoxic effects on oral tissues.

Methods:Zebrafish embryo toxicity was evaluated through mortality and hatching rates, measurement of heart rate, morphological examination for malformations, and detection of reactive oxygen species (ROS) levels using fluorescent staining.

Results: Both Calibra veneer and Variolink cements did not induce mortality in zebrafish embryos, with a survival rate exceeding 90% in all groups. Hatching rates were consistent across treated and control groups. Heart rate measurements at 72 hours post-fertilization (hpf) revealed no significant alterations in atrial and ventricular contractions compared to the control group. Morphological analysis showed normal architecture in embryos and larvae treated with either cement, with no malformations observed. ROS detection indicated lower levels in Variolink-treated larvae compared to Calibra veneer-treated larvae, suggesting less oxidative stress induction by Variolink.

Conclusion: The findings suggest that both Calibra veneer and Variolink cements have minimal cytotoxic effects on zebrafish embryos and larvae. However, Calibra veneer induced higher ROS levels compared to Variolink, indicating a potential difference in oxidative stress induction between the two cements. Further studies are warranted to elucidate the underlying mechanisms and translate these findings to clinical relevance.

1. Introduction

Cosmetic dentistry has gained popularity over the years due to an increase in the desire for a harmonious and aesthetic smile, combining beauty and function. [1] In this context, a survey concluded that ninety one percent of practitioners recommended the standard use of veneers in the field of aesthetics to treat various problems such as discoloured or mal-aligned teeth.[2]

However, selecting an appropriate luting agent for indirect restorations remains a pivotal factor influencing their long-term clinical success. Studies have shown that for long-lasting retention, these materials must have low solubility and high strength [3]. Obtaining sufficient polymerisation of the adhesive resin cement is the first stage in assuring these qualities for restoration longevity. [4]

Among the different materials available in market, resin cements have been used widely owing to some advantages such as excellent mechanical and handling properties, good aesthetics and successful binding to enamel.[1] Light-cured resin cements have become the first choice for veneer cementation due to their higher colour stability and controlled working time [1]

Despite several advantages, these cements have certain drawbacks such as formation of a thickened film at margins and possible micro-leakage as a result of polymerization shrinkage. Ideally, a prerequisite for veneer cementation includes use of biocompatible materials with minimal cytotoxic effects on the oral cavity [1].

In-vitro studies conducted in the past have shown that at times incomplete monomer conversion can result in local and systemic adverse effects by leaching out into the adjacent tissues. According to literature, the phenomenon of uncured monomer release begins during the polymerization reaction and can last up to 21 days [1]**.**

In-vitro cytotoxicity tests are widely used to predict clinical outcomes as they are highly reproducible, less expensive and suitable for evaluating biological properties of dental materials. [1]

Zebrafish (Danio rerio) is a commonly used model organism in various fields of research, including dental studies [5–8]. Zebrafish possess several advantages as a model organism, such as their small size, rapid development, transparency of embryos, and genetic tractability. These characteristics make them particularly suitable for studying various aspects of dental research, including tooth development, regeneration, and oral disease modelling [9–12]. Zebrafish continuously develop replacement teeth throughout their lifespan, which makes them an excellent model for studying tooth development and regeneration [13,14]. Researchers can investigate the genetic and molecular mechanisms underlying tooth formation by manipulating specific genes and observing the resulting phenotypes [15–17]. This can provide insights into the molecular pathways involved in human tooth development and regeneration. Zebrafish have the remarkable ability to

regenerate lost or damaged teeth throughout their lives. By studying the regenerative processes in zebrafish, researchers can gain insights into the cellular and molecular mechanisms that enable tooth regeneration [18–21][14–17]. This knowledge can potentially be applied to enhance the regenerative capacity of human teeth, which could have implications for dentistry and oral health treatments.Oral disease modeling: Zebrafish can be used to model various oral diseases, including dental caries, periodontal disease, and oral cancer. By introducing specific genetic mutations or exposing zebrafish to disease-inducing agents, researchers can study the pathogenesis of these oral diseases and test potential therapeutic interventions [22–25]. Zebrafish's optical transparency during early developmental stages allows for real-time visualization of disease progression and the effects of treatments. Zebrafish can serve as a screening platform for identifying potential drug candidates for dental-related conditions [26–28][29]. By using zebrafish models of oral diseases, researchers can screen libraries of chemical compounds to identify molecules that can modulate disease progression or promote tooth regeneration [30–33]. Zebrafish-based drug discovery approaches can offer a cost-effective and efficient way to identify promising therapeutic candidates. Overall, zebrafish provide a valuable model system for dental research due to their genetic amenability, regenerative capacity, and optical transparency [21,34–36]. By utilizing zebrafish, researchers can gain insights into tooth development, regeneration, oral disease pathogenesis, and potentially discover new therapeutic approaches for dental-related conditions.

The aim of the present study was to evaluate the cytotoxic effects of two different resin-based veneer luting cements namely Calibra veneer and Variolink cement in in-vivo zebrafish model. The null hypothesis of this study is that the tested cements present no cytotoxic effects on oral tissues.

2. Materials and Methods

The study was performed after clearance from the Institutional Review Board[SRB/SDC/ENDO-2101/23/052]

2.1. Origin and maintenance of zebrafish

Adult zebrafish (Wild type – AB strain, 4 months old) were purchased from a local aquarist (NSK aquarium, Kolathur, Tamil Nadu, India). The male and female fishes were separated, maintained in our facility under the following condition in a 10 L glass tank: 28.5˚C, with a 14/10 h light/dark cycle [37–40]. The fish were fed t hree times a day, with live brine shrimp (*Artemia salina*). The fishes were acclimatized for 1 month, later the fishes were utilized for breeding, and embryos were collected and used for the following experiments [37]. The collected embryos are further analyzed under a microscope, unfertilized embryos are discarded, whereas the fertilized embryos are taken in a six-well plate and incubated in E3 medium.

2.2. Zebrafish embryo toxicity test

For the developmental toxicity assessment studies, 4 hpf embryos were used, the exposure was carried in a 6 well plate containing untreated larvae as the control, Calibra veneer cement and Variolink cement. Around 15 embryos/well were used with 3 mL of E3 medium. The exposure was non-static and renewed every 24 h with the fresh treatment solution throughout the exposure period (4 hpf to 96 hpf). All the experiments were carried out in triplicates. Parameters such as survival and malformation were observed during this period, and calculations were presented at the end of 96 hpf [41].

2.3. Intracellular ROS assay

DCFDA (2',7'-dichlorofluorescin diacetate) is a fluorescent probe commonly used to assess oxidative stress levels in cells and tissues [42][40]. It can be used to measure the generation of reactive oxygen species (ROS) within a sample. If you are interested in conducting a DCFDA experiment in zebrafish larvae, here's a general outline of the procedure. Preparation of DCFDA solution. Prepare a stock solution of DCFDA by dissolving it in a suitable solvent, such as dimethyl sulfoxide (DMSO), to a concentration of typically 10-100 mM. Protect the stock solution from light and store it at -20°C. Larval zebrafish handling: Obtain zebrafish larvae at the desired developmental stage (e.g., 3-5 days post-fertilization). Handle the larvae with appropriate care and follow ethical guidelines for animal experimentation [43–45][41–43]. Keep the larvae in an appropriate fish facility under controlled conditions (temperature, lighting, water quality, etc.). Treatment groups: Design your experiment with appropriate treatment groups. For example, you may have control larvae and experimental groups exposed to specific conditions or treatments that induce oxidative stress [38][34]. Incubation with DCFDA: Prepare a working solution of DCFDA by diluting the stock solution in an appropriate buffer or medium. The concentration of DCFDA in the working solution will depend on the specific requirements of your experiment [46][44]. Typically, concentrations between 5-20 μM are used. Incubate the zebrafish larvae in the DCFDA working solution for a defined period, often 30 minutes to 1 hour, at an appropriate temperature (typically 28-32°C). Wash and imaging: After the DCFDA incubation period, carefully remove the larvae from the DCFDA solution and wash them with fresh buffer or medium to remove any excess probe [47][45]. Gently transfer the larvae to a suitable imaging chamber or dish. Imaging and analysis: Using a fluorescence microscope or imaging system, capture images of the zebrafish larvae [48][46]. DCFDA is a non-fluorescent compound that becomes fluorescent upon oxidation by ROS, resulting in the emission of green fluorescence. Set appropriate excitation and emission

wavelengths for DCFDA detection. Quantify the fluorescence intensity using image analysis software to compare oxidative stress levels between different treatment groups [48][47].

2.4. Statistical analysis

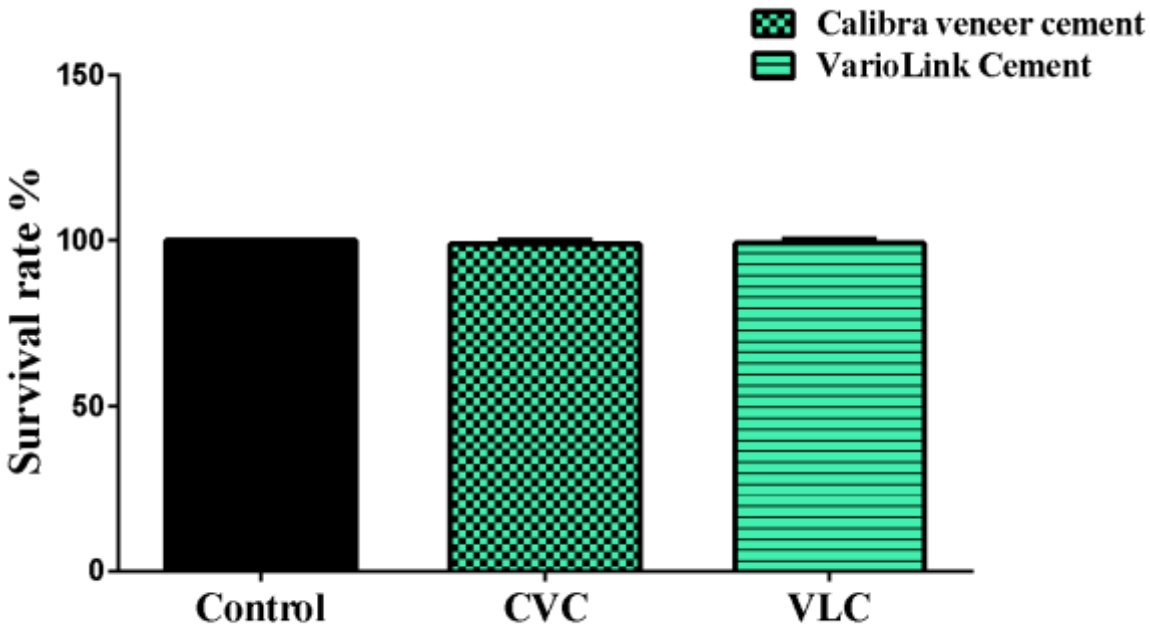
The data were presented as the mean of triplicates with a standard deviation. GraphPad Prism software (Ver 5.03, CA, USA) was used for statistical analysis. One-way ANOVA was performed and Tukey's post-hoc test was used to find levels of significance between control and other groups.

3. Results and Discussions

Zebrafish embryo toxicity test

3.1 Mortality and hatching rate

The Calibra veneer cement and Variolink cement did not cause mortality in zebrafish embryos. As shown in Fig. 1, the Survival rate was found to be more than 90% in all the group. Additionally, the hatching rate was calculated at 48 hpf. It was observed that 100% of the zebrafish embryo emerged out of their chorions in the control group. However, a similar in the hatching rate was observed all the other treated group.


Calibra veneer cement
VarioLink Cement
Survival rate %
150
100
50
0
Control
CVC
VLC

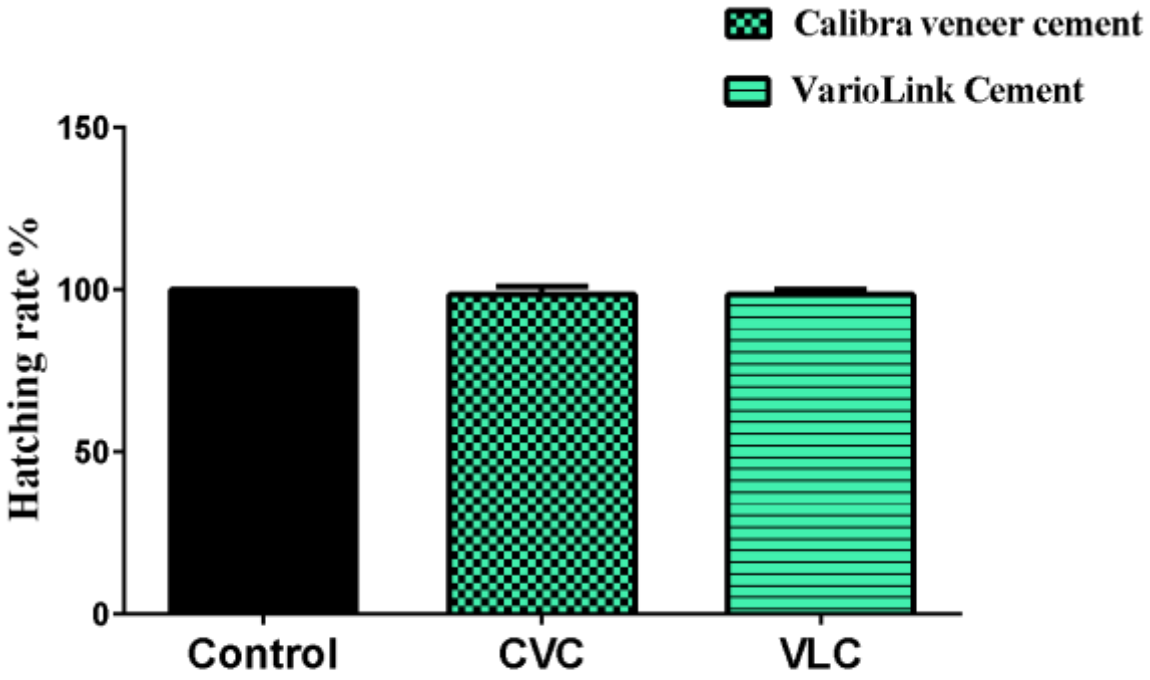

Calibra veneer cement
VarioLink Cement
Hatching rate %
150
100
50
0
Control
CVC
VLC

Figure.1. Survival and Hatching rate of the zebrafish larvae exposed to Calibra veneer cement and Variolink cement

3.2 Measurement of heart rate

The heart rate of zebrafish embryos was evaluated at 72 hpf, to assess the toxicity of the treatment group. The atrial and ventricular contractions were counted and recorded under a microscope for 1 min and average heart beats per minute were reported. The result shows that all the groups of Calibra veneer cement and Variolink cement did not significantly alter the heart beat rate of the zebrafish embryos when compared to the embryos from the control (untreated) group (Fig. 3,4).

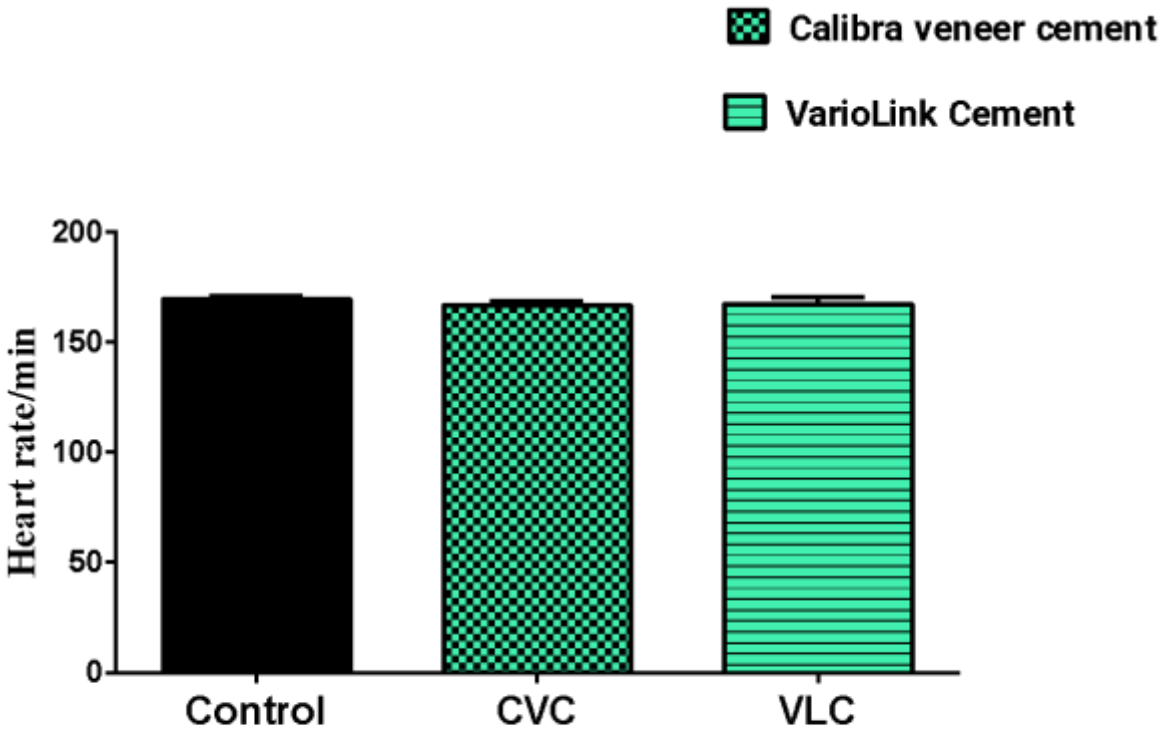


Figure.2. Heart rate of the zebrafish larvae exposed to Calibra veneer cement and Variolink cement

3.3. Morphological malformation

The Calibra veneer cement and Variolink cement treated zebrafish embryos and larvae exhibited normal morphological architecture under the microscope (Fig. 2). No malformations such as yolk sac edema and bent spine are formed in the larvae.

Figure.3. Morphology of the zebrafish larvae exposed to Calibra veneer cement and Variolink cement

3.4 Reactive oxygen species detection

Using the fluorescent stain, the level of ROS in the head region was visualized in the larvae. The increase in fluorescent intensity indicates the increase in ROS level in larvae. But this condition was effectively low when the larvae were treated with Variolink cement. The fluorescent intensity was noted as similar to the control group. Meanwhile, Calibra veneer cement increased the fluorescent intensity which indicates the ROS level. These results suggest that Variolink cement induces no oxidative stress condition compared to the Calibra veneer cement.

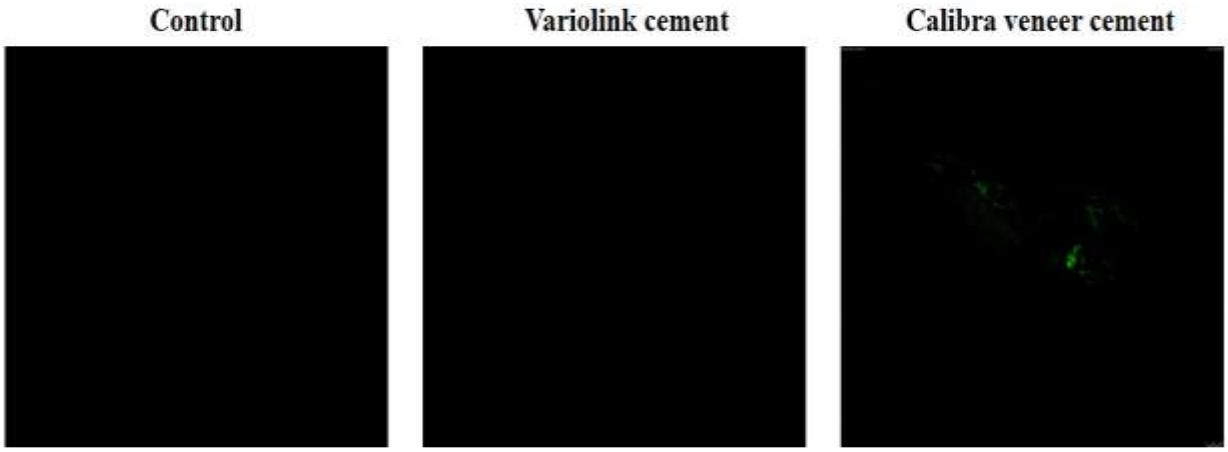


Figure 4. The DCFDA experiment in the zebrafish larvae exposed to Calibra veneer cement and Variolink cement. The green fluorescent indicates the presence of oxidative stress in zebrafish larvae.

4. Conclusion

The results shows Calibra veneer cement showed oxidative stress condition to the larvae compared to the Variolink cement when exposed to the zebrafish larvae

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