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Original Article

Dentistry Section

A Comparative Evaluation of Cytotoxic Effects of Two Different Self-adhesive Luting Resin Cements: An In-vitro Study

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ABSTRACT

Introduction: Resin cements are commonly used for luting porcelain inlays, porcelain laminate veneers, resin-bonded metallic prostheses, and ceramic restorations. However, the monomers found in these cements- such as Bisphenol-A-Glycidyl Methacrylate (Bis-GMA), Urethane Dimethacrylate (UDMA), Diethylene Glycol Dimethacrylate (DEGDMA), Triethylene Glycol Dimethacrylate (TEGDMA), and 2-Hydroxyethyl Methacrylate (HEMA) has demonstrated cytotoxic effects. When these monomers come into direct contact with fibroblasts, they can lead to pulp tissue damage and induce cell death.

Aim: To evaluate and compare the cytotoxic effects of two self-adhesive luting resin cements SoloCem (Coltene) and SmartCem 2 (Dentsply).

Materials and Methods: The present in-vitro cytotoxic study was conducted in SDM Institute of Dental Sciences, Dharwad, Karnataka, India. for two years from October 2016 to October 2018. Two luting resin cements SoloCem and SmartCem were tested in this study. Ten samples for each group (SoloCem, SmartCem and control) were taken. The specimens were immersed in a culture medium. Mouse fibroblasts were cultured. The culture medium, containing material extracts was evaluated. The cell viability was assisted using MTT assay. Colony formation assay was done to evaluate morphological changes. The statistical analysis was done by using Graph pad prism version 3.02. A p value of <0.05) was considered significant. Statistical analysis done by the One-way ANOVA analysis and post-hoc test of variance among the groups.

Results: There was a significant difference in Optical Density (OD) values between the three groups when the three groups were compared p<0.001**. According to post-hoc analysis it was seen that Smart CEM significantly promotes higher cell survival compared to Solo CEM 2 p<0.001**. Both SoloCem and SmartCem 2 significantly reduced cell viability when compared to the control group p<0.001** and p=0.027, respectively. These results indicate that Smart cem resin cement promoted better cell viability while Solo Cem 2 led to increased fibroblast cell death.

Conclusion: Based on the study findings, SmartCem was found to be the more biocompatible luting resin cement to the pulp and fibroblasts than Solo which Cem which has shown less cell survival rate. So, in general smart cem 2 cement can be considered as a safe resin cement to be used for cementation of all fixed prosthesis.

Keywords: Biocompatibility, Cell viability, Culture medium, Mouse fibroblast, Optical density

INTRODUCTION

The biological compatibility of dental materials is crucial to prevent or minimise irritation or damage to the pulp tissue. The cytotoxicity and biocompatibility of materials used in dentistry have been extensively investigated using various cell cultures and in deep cavities, both with and without pulp exposure [1]. The latest advancement in the “resin cement family” is the introduction of self-etching resin cements, which do not require any pretreatment of the tooth surface. These cements offer several clinical advantages over traditional resin cement systems. Additionally, many of them are now provided in auto-mix delivery systems, streamlining their application by removing the need for a triturator in the operatory [2]. Following crown preparation, the removal of the enamel layer exposes the dentin surfaces and dentinal tubules to the oral environment [3].

One of the main disadvantages of resin-based materials is their potential to cause sensitivity reactions. Both in-vivo and in-vitro studies have shown that monomers released from these materials can lead to varying degrees of tissue damage, ranging from gingival margin retraction to inflammation extending to the pulp, and even cell death [4]. Bis-GMA, UDMA, DEGDMA, TEGDMA, and 2-HEMA, along with additional components such as co-initiators, photo-initiators, inhibitors, and color pigments, are commonly used in resin-based materials. These substances can interfere with cellular metabolism and may lead to adverse clinical effects [5]. Residual monomers, which result from the incomplete polymerisation of monomers, have the potential to cause irritation, inflammation, and allergic reactions in the oral mucosa [6]. Cell culture testing of dental materials is relatively easy to conduct, reproducible, and cost-effective, with the added benefit of allowing precise control over experimental conditions [7]. A previous study evaluated the effects of cements on murine macrophages and showed that the cements demonstrated heightened cytotoxicity when not photoactivated, emphasising the critical role of proper photoactivation in clinical practice [8].

In another study, the cytotoxic effects of several resin cements examined on different human cell lines. The findings demonstrated notable variations in cytotoxicity levels among the materials, with certain cements showing pronounced cytotoxic effects [9]. Another study investigated the impact of heat treatment before photopolymerisation on the cytotoxicity of self-adhesive resin cements. The results showed that preheating the cements to 60°C significantly reduced their cytotoxicity, indicating that heat treatment could be a promising approach to improve their biocompatibility [10]. Overall, there is a need to reassess the physicochemical and biological properties of materials currently used in restorative dentistry, as many of them seemingly fail to meet the necessary standards for safety and durability [11].

In recent years, an increasing number of luting resin cements has been introduced to the market. Many of these cements contain

components such as HEMA and TEGDMA, which complicate the evaluation of their biocompatibility and safety. Therefore, assessing their cytotoxicity is crucial to support the development and adoption of safer resin cements. The present study aimed to evaluate and compare the cytotoxic effect of two self-adhesive luting resin cements SoloCem (Coltene) and SmartCem 2 (Dentsply).

MATERIALS AND METHODS

The present in-vitro study was conducted at the SDM Institute of Dental Sciences, Dharwad, Karnataka, India, over a period of two years starting in October 2016, the cytotoxicity of two self-adhesive resin luting cements was evaluated.

Sample size calculation: The sample size for each group was set at 10 specimens, based on methodologies used in similar in-vitro studies (Malkoç MA et al., 2014) [12].

- **group 1:** SoloCem (Coltene/Whaledent AG, Switzerland), a self-adhesive resin cement supplied in dual auto-mix syringes. Its composition includes methacrylate, zinc oxide, and dental glass. The product used had the lot number H15869.
- **group 2:** SmartCem 2 (Dentsply, USA), also a self-adhesive resin cement available in dual auto-mix syringes. It contains UDMA, di- and tri-methacrylate resins, phosphoric acid-modified acrylate resins, barium boron fluoroaluminosilicate glass, camphorquinone, phosphine oxide photoinitiators, titanium dioxide, and silicon dioxide. The product used had the lot number 160214.
- **group 3:** A control group consisting of cell culture medium included to compare cell death levels with those exposed to extracts from the two self-adhesive cements.

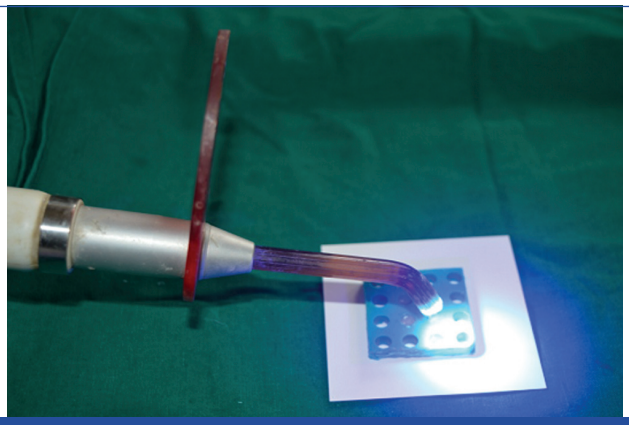
Study Procedure

Test sample preparation: To standardise the test samples, all specimens were prepared as cylindrical blocks measuring 5 mm in diameter and 4 mm in length [Table/Fig-1,2].

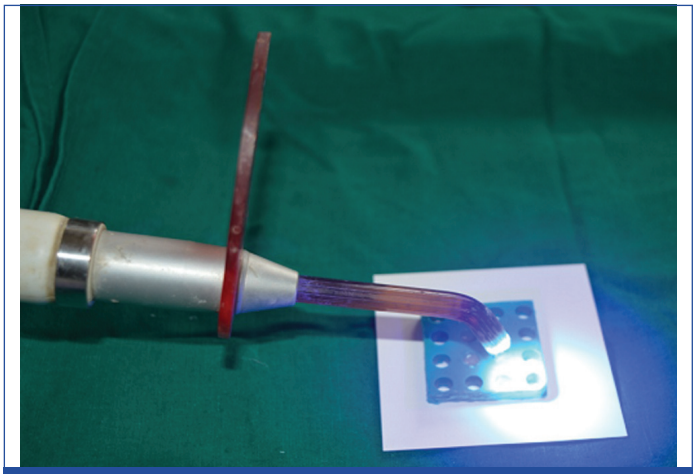
[Table/Fig-1]: group 1 Resin luting cement (SoloCem) is injected in a mould.

[Table/Fig-2]: group 2 resin luting cement (Smart cem) is injected in a mould.

Luting resin cement (SoloCem) was injected into the mold and photoactivated for 40 seconds. Similarly, SmartCem 2 was injected into a separate mold and also photoactivated for 40 seconds [Table/Fig-3,4]. An Light Emitting Diode (LED) curing light (Elipar FreeLight 2, 3M ESPE, St. Paul, MN, USA) with an output intensity of 550 mW/cm^2 was used for this process. The exposure time of 40 seconds was based on the manufacturer's recommendation for proper photopolymerisation.

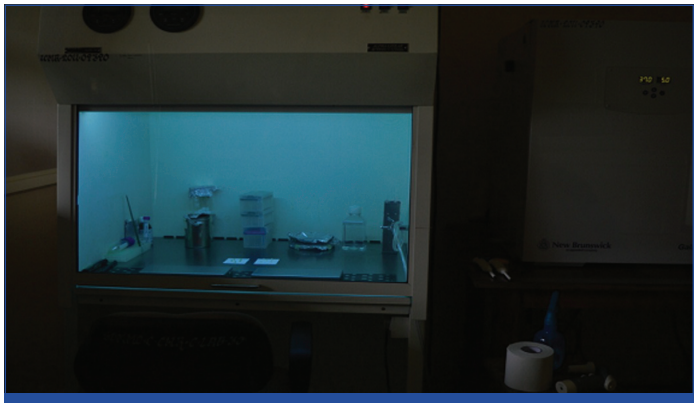


[Table/Fig-3]: The photopolymerisation of SoloCem resin luting cement (group 1) using 3M ESPE deep cure LED curing light for 40 seconds.



[Table/Fig-4]: The photopolymerisation of SmartCem resin luting cement (group 2) using 3M ESPE deep cure LED curing light for 40 seconds.

After curing, the samples were removed from the molds and sterilised by exposure to Ultraviolet (UV) light for 20 minutes in UV Spectrum uses UV-C light (wavelength ~254 nm), which is effective in killing or inactivating microorganisms [Table/Fig-5].

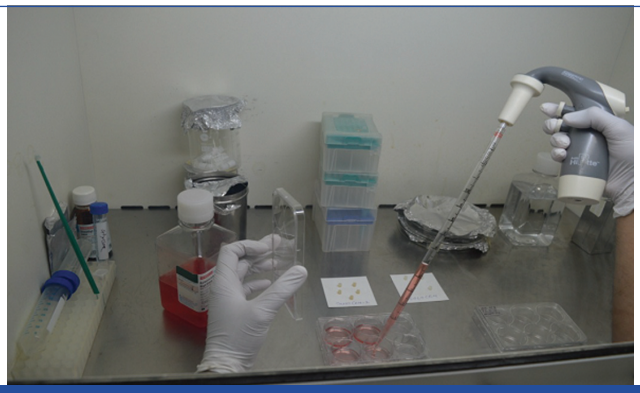


[Table/Fig-5]: Resin cements sterilisation by using Ultraviolet (UV) light for 20 minutes.

Cell culture: The specimens were immersed in 7 mL of culture medium having mouse normal fibroblast cells (sourced from NCCS, Pune) cultured at 37°C in a humidified atmosphere comprising 5% CO_2 and 95% air. These cells were grown in Dulbecco's Modified Eagle Medium (DMEM) High Glucose (HIMEDIA Laboratories, Mumbai), supplemented with 10% foetal bovine serum and 1% Antibiotic-antimycotic solution (both from HIMEDIA Laboratories,

Mumbai). For 24 hours at 37°C to facilitate the leaching of residual monomers or any cytotoxic substances [12].

Cell viability MTT assay: Cell viability was assessed using a colorimetric MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide). Briefly, NIH 3T3 fibroblasts were seeded at a density of 2×10^5 cells per well in separate 6-well plates and cultured until they reached 60-70% confluence [Table/Fig-6]. SoloCem and SmartCem 2 samples were placed in two separate 6-well plates, while the control group was maintained without any cement exposure. After 24 hours of incubation, 200 µL of MTT solution (5 mg/mL) was added to each well, and the plates were incubated for an additional two hours at 37°C.



[Table/Fig-6]: NIH-3T3 cell seeding in 6 well plates.

The Optical Density (OD) was measured at a wavelength of 450 nm using an Epoch Microplate Reader (BioTek Instruments, Highland Park, VT, USA). MTT assay [Table/Fig-7]. The recorded OD values were used directly to calculate the percentage of viable cells. Cell viability from the MTT assay was determined using the formula:

[Table/Fig-7]: Epoch Microplate Reader (Biotek Instruments, highland Park, VT,USA). (MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide) assay). SoloCem (Coltene/Whaldent AG,Switzerland) as group 1 and SMART CEM 2 (DENTSPLY, USA) as group 2 and control group as group 3 were evaluated.

Cell viability (%)=(OD_{550} of treated cells/OD_{550} of control cells)×100

For example, if the OD reading of the control (untreated) cells is 0.5, and the OD of the treated cells is 0.3, applying the formula gives:

Cell viability (%)=(0.3/0.5)×100=60%

This means that 60% of the cells remained viable after treatment compared to the untreated control. The remaining 40% reduction in viability indicates cytotoxicity - the extent to which the treatment has reduced cell survival. It's important to clarify that 60% is the actual cell viability, while 40% represents the loss of viability, or the cytotoxic effect of the treatment. Both values give useful information: viability tells us how many cells survived, and cytotoxicity tells us how many cells were affected by the treatment [13].

Colony formation assay: To evaluate morphological changes, cells were cultured until they reached approximately 80% confluence. They were then trypsinised and seeded in 6-well plates in triplicate at a density of 500 cells per well. The cells were incubated for two days at 37°C to allow for adherence and growth and the cement samples were placed in each well plates. After 48 hour of incubation, the changes in the cell morphology were captured under objective of Motic inverted microscope with 10 MP resolution camera with the help of motic image PLUS 2.0 [Table/Fig-8]. The cell survival rates are typically measured using in-vitro cytotoxicity assays and an inverted optical microscope plays a key role in observing and quantifying the cells during or after these assays. Inverted optical microscopes were essential for visualising and assessing cell health. The inverted optical microscope is used to observe cell morphology. Cytotoxicity of resin materials is judged based on cell morphology, attachment, and viability counts. Healthy cells appear spread out and attached, while dead or unhealthy cells may shrink, round up, or detach. In stained assays like Trypan Blue, counts were digitally assessed. Magnification kept commonly at 100x-400x magnification [14].

[Table/Fig-8]: Motic inverted microscope.

STATISTICAL ANALYSIS

The data obtained during the course of the study was subjected to statistical analysis. The statistical analysis was done by using Graph pad prism version 3.02. Differences between mean values were statistically analysed by using One-way ANOVA and Post-Hoc tests.

RESULTS

Each group has 10 observations (N=10), and the OD values at 550 nm reflect the level of viable cells after treatment. OD value at 550 nm is shown in [Table/Fig-9].

In SoloCem the OD reading 0.0404 showing low absorbance indicating lesser viability and decreased cell survival rates. In SmartCem 2 the OD reading 0.0620 showing high absorbance and greater viability and increased cell survival rates. Control group: 0.0740 was baseline for comparison. The cell viability for SoloCem was 57% and 85% for SmartCem

According to ANOVA analysis, there was a significant difference between the three groups. $p<0.0001^{**}$ [Table/Fig-10]. The statistical results confirm that SmartCem promotes higher cell survival compared to SoloCem $p<0.001^{**}$. Both SoloCem and SmartCem 2 significantly reduced cell viability when we compared to the control group $p<0.001$ and $p=0.027$, respectively [Table/Fig-11]. SoloCem had more cytotoxic effects on cultured cells showing 57% of cell viability than Smart cem 2 which showed 85% cell viability when compared to control group respectively.

Phase contrast mode (if available) helps better visualise transparent cells without staining. Cell survival rate was calculated by the control group there was no noticeable changes in cell morphology or signs of cell death were observed. Cells retained their normal structure and distribution [Table/Fig-12a-c]. SmartCem resin cement showed approximately 85% of cell survival rate. Cells showed relatively minor morphological changes, indicating low cytotoxicity [Table/Fig-12b]. SoloCem resin cement showed about 57% cell survival rate. Cells exhibited severe morphological changes, such as shrinkage and detachment, indicating moderate cytotoxic effects [Table/Fig-12c].

Groups	N	Mean	Std. Deviation	Std. Error	95% Confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
1 SoloCem	10	0.0404	0.00107	0.00034	0.0396	0.0412	0.04	0.04
2 SmartCem	10	0.0620	0.01677	0.00530	0.0500	0.0740	0.04	0.09
3 control	10	0.0740	0.00000	0.00000	0.0740	0.0740	0.07	0.07
Total	30	0.0588	0.01696	0.00310	0.0525	0.0651	0.04	0.09

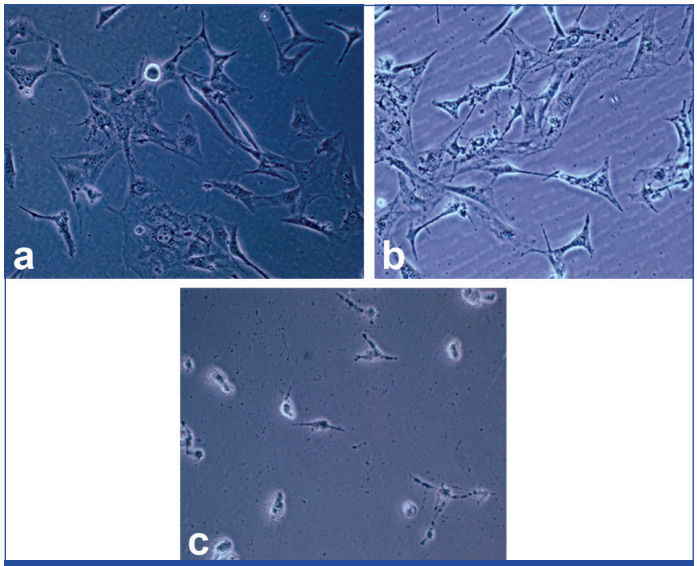
[Table/Fig-9]: Descriptive statistics for OD readings at 500 nm of tested materials.

Comparison of groups	Sum of Squares	df	Mean square	F	Sig.
Between groups	0.006	2	0.003	30.789	0.000
Within groups	0.003	27	0.0001		
Total	0.008	29			

[Table/Fig-10]: Results of ANOVA analysis.
ANOVA=Analysis of variance; Significance: p<0.0001 (highly significant)

(I) groups	(J) groups	Mean Difference (I-J)	Std. Error	Sig.	95% confidence interval	
					Lower bound	Upper bound
1	2	-0.02160 (*)	0.00434	0.0001	-0.0324	-0.0108
	3	-0.03360 (*)	0.00434	0.0001	-0.0444	-0.0228
2	1	0.02160 (*)	0.00434	0.0001	0.0108	0.0324
	3	-0.01200 (*)	0.00434	0.027	-0.0228	-0.0012
3	1	0.03360 (*)	0.00434	0.000	0.0228	0.0444
	2	0.01200 (*)	0.00434	0.027	0.0012	0.0228

[Table/Fig-11]: Post-hoc tests for group 1(SoloCem), group 2 (smart cem) and group 3 (control).
* The mean difference is significant at the .05 level



[Table/Fig-12]: a) Cell survival using Motic inverted microscope in the control group. No noticeable changes in cell morphology or signs of cell death were observed. Cells retained their normal structure and distribution; b) Cell survival determined using Motic inverted microscope with the resin luting cement SmartCem has about 85% of the cell survival rate; c) Cell survival determined using Motic inverted microscope with the resin luting cement Solo Cem has about 57% of the cell survival rate.

DISCUSSION

The present study aimed to evaluate the cytotoxic effects of different resin cements and determine which one is safer and less toxic for clinical use. Two dual-curing, self-adhesive resin cements were selected: SoloCem (Coltene), a newer-generation cement, and SmartCem 2 (Dentsply), an older formulation. Modern resin-based cements generally have a composition similar to that of composite resins. In this study, Solo CEM, the newer resin cement, was found to exhibit higher toxicity and greater levels of cell death. This increased cytotoxicity is likely attributed to its chemical composition, which includes organophosphonates, HEMA, and the 4-Methacryloxyethyl Trimellitic Anhydride (4-META) system. Additionally, phosphonate-based cements often contain silanated quartz filler, which may also contribute to their toxic effects [15]. Since most of the prepared tooth surface consists of dentin, resin cement inevitably comes into contact with both dentin and gingival tissues during cementation. The monomers present in these cements can cause irritation and exert toxic effects on these tissues. In the present study, an LED curing light was used with an exposure time of 40 seconds, following the manufacturers' recommended protocol for photopolymerisation. Under these conditions, it was anticipated that minimal unreacted monomers would remain, thereby reducing the risk of leaching and associated toxicological effects. Previous literature has investigated the elution of monomers such as 2-HEMA and TEGDMA from Resin-Modified Glass Ionomer Cements (RMGICs) and compomers when cured using halogen and LED Light-Curing Units (LCUs). It was concluded that curing with halogen LCUs resulted in greater cytotoxicity and lower cell viability compared to LED curing, likely due to a higher amount of residual monomer [12].

A study conducted by de silva confirmed that both RelyX U200 and seT PP were more cytotoxic to macrophages when chemically activated rather than photoactivated; notably, RelyX U200 maintained better cell viability over time, which aligns with findings in odontoblast-host cell models. The lack of HEMA in RelyX U200 and its ability to approach neutral pH upon adequate light activation may underlie this improved biocompatibility. Conversely, seT PP- particularly under chemical activation- demonstrated lower cell viability and significantly impaired macrophage phagocytosis. This is likely due to its low monomer conversion and reduced dependence on light activation, which impair its performance. So their clinical performance depends heavily on adequate polymerisation, with studies indicating that monomer conversion rates after 20 seconds of light exposure can be as low as 37%- rising only to 58% after 40 seconds- suggesting that manufacturer-recommended light-curing protocols may be inadequate. In summary, these findings underscore the critical role of effective photoactivation in maximising the biocompatibility of self-adhesive resin cements. When properly light-cured, both RelyX U200 and seT PP demonstrate reduced cytotoxicity and less disruption of macrophage function [8].

A study by Diemer F et al., evaluated and compared the cytotoxic effects of several commonly used dental resin cements on various human cell lines, including fibroblasts and osteoblasts-cells critical for dental tissue health and repair concluded that all tested cements showed some degree of cytotoxicity, but the severity varied by cement type and the type of human cells exposed. Osteoblasts (bone-forming cells) were more sensitive than fibroblasts, indicating that resin cements may pose a greater risk when in contact with bone or deeper tissues. The cytotoxicity was largely attributed to monomer release (such as Bis-GMA, UDMA, and TEGDMA), especially when cements were not fully polymerised. Direct contact between the resin and cells led to greater toxicity compared to indirect exposure (e.g., through cement-conditioned media). Diemer F et al., provided clear evidence that while resin cements are essential in modern dentistry, they carry biological risks that vary by product and usage. The findings stress the importance of biocompatibility testing, informed material choice, and optimised clinical techniques to ensure patient safety [9].

In this study, curing was performed following standardised protocols to minimise the presence of residual monomers. The evaluation

of dental materials using cell culture techniques offers several advantages. These methods are relatively simple, reproducible, and allow for strict control of experimental conditions. A significant benefit of cell culture testing is the absence of ethical concerns, along with the ease of standardisation. Such in-vitro methods present a viable alternative to traditional animal testing, which is often expensive, ethically controversial, and subject to numerous uncontrollable variables. Therefore, cell culture-based assessments are not only efficient but also ethically and scientifically favourable for evaluating the biocompatibility of dental materials [7]. This study incorporated cell culture extract testing, the MTT assay, and a colony formation test to assess cell viability. A key focus was placed on the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay, which is used to evaluate the adverse intracellular effects on cellular metabolic activity. The MTT assay is well-established, straightforward to perform, and continues to be widely utilised in laboratories around the world due to its reliability and effectiveness [16]. In-vitro test methods using cell lines are commonly employed to assess the cytotoxicity of dental materials. According to national and international guidelines established by the International Organisation for Standardisation (ISO), all dental materials must undergo biocompatibility testing before clinical application. Compared to animal testing, which is often time-consuming, costly, and subject to public scrutiny, in-vitro cytotoxicity tests offer several advantages. These include greater ease in controlling experimental variables, which are often difficult to manage in in-vivo studies [17]. Cell viability was assessed using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide), a well-established and widely accepted method for evaluating cell survival [12]. This assay was chosen due to its reliability and effectiveness. NIH 3T3 mouse fibroblasts were selected for the study as they serve as a suitable alternative model for in-vitro cytotoxicity screening, closely resembling the fibroblast cells found in gingival and pulpal tissues of the tooth [18]. Assessing fibroblast cell responses to resin cement materials is essential, and numerous research groups have utilised fibroblasts in their experiments. A past study demonstrated that the L929 cell line produces results comparable to those of primary human gingival fibroblasts, making it a viable alternative model for in-vitro screening of gingival toxicity. Their findings also indicated that variations in the experimental setup had a greater impact on toxicity outcomes than the source of the fibroblast cells [19]. Geurtsen W et al., examined the cytotoxic effects of composite resins using permanent 3T3 cells and three primary human oral fibroblast cultures. Their study also reported that Bis-GMA exhibited cytotoxicity when tested on human pulp fibroblasts in-vitro. Similarly, Meral et al. observed comparable findings while evaluating the cytotoxicity of three different luting cements using L929 fibroblast cells and the MTT assay. One of the key photoinitiators, camphorquinone, was detected in significant amounts in aqueous extracts of resin-based materials and was associated with moderate cytotoxic effects [20]. A study demonstrated that TEGDMA causes a significant depletion of intracellular glutathione (GSH) levels and induces severe cytotoxicity in cultures of Human Periodontal Ligament Fibroblasts (HPLF). The cytotoxicity of the tested monomers ranked as follows: Bis-GMA>UDMA>TEGDMA [20]. Another study investigated the cytotoxic and genotoxic effects of UDMA, commonly used as a monomer at a concentration of 1 mM, and TEGDMA, a typical co-monomer, at 5 mM-both individually and in combination [21]. These findings were supported by a study conducted by Atsumi T et al., which utilised permanent human submandibular duct cells [17]. According to Klein-Júnior CA et al, raising resin temperature generally promotes better monomer conversion and thus reduces cytotoxicity. However, in this study, preheating to 39°C did not significantly enhance polymer conversion or cell viability, likely because the temperature was lower than in studies using 54-60°C. Applying heat near the pulp (e.g., warm air at ~50-70 °C) can raise dentin temperature by 5-16°C. While such increases may risk pulpal inflammation or damage, existing evidence suggests that a rise of up to ~15°C is not always harmful. Regardless of pre-heating, all cements exhibited high cytotoxicity, especially in the first 24 hour, with minimal cell migration and in many cases, cell death. Even diluted extracts caused significant cytotoxic effects. Klein-Júnior CA et al., found that preheating to 39°C did not reduce the cytotoxicity of self-adhesive resin cements in-vitro- high toxicity levels remained. While heat can improve polymerisation, the temperature used here was insufficient, and concerns remain about pulpal safety [10].

Overall, Smart cem 2 appears to be suitable for use in prosthodontic applications. Established protocols are available for the definitive placement of indirect restorations using commonly used dental cements. However, to enhance the validity and applicability of these findings, future research should be conducted on a broader scale, incorporating more clinically relevant conditions. It is also important to evaluate newer resin luting cements to expand the understanding of their biocompatibility.

Limitation(s)

A key limitation of this study was the challenge in accurately determining the material properties of the tested substances. Furthermore, the materials used were not ideally suited for handling biological samples, such as cells and fluids, which may have influenced both the experimental procedures and the results.

CONCLUSION(S)

Based on the findings of the present in-vitro study, the following conclusions can be drawn: SMART CEM, a resin luting cement, demonstrated higher cell viability at approximately 85%, indicating better biocompatibility. In contrast, SOLO CEM showed reduced cell viability of around 57% when compared to the control group. Among the tested resin-based cements, SMART CEM proved to be the less cytotoxic and more biocompatible, making it a safer option for use in various dental applications. Future research should focus on evaluating the long-term biological effects of resin cements to further ensure their safety and effectiveness in clinical use.

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