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Original Article

In vivo biocompatibility of Resilon compared with gutta-percha in a pre-clinical model

Miguel Cardoso[1], Rodrigo F. Marques[1], Maria Francelina Lopes[2], António S. Cabrita[1], João Miguel Santos[3]

[1]Departments of Experimental Pathology, and [2]Experimental Surgery, Faculty of Medicine of the University of Coimbra, Rua Larga, 3004-504, [3]Department of Dental Medicine, Stomatology and Maxillofacial Surgery, Faculty of Medicine of the University of Coimbra, Av. Bissaya Barreto, 3030-005, Coimbra, Portugal

ABSTRACT

Background: The aim of this study was to investigate *in vivo* biocompatibility of Resilon, compared with gutta-percha, at short and long-term following implantation in a rat subcutaneous implantation model.
Materials and Methods: Male Wistar rats were implanted subcutaneously with either Resilon or gutta-percha or were sham controls. Tissues were harvested at 8 days or 60 days after implantation and were evaluated histologically for inflammation and fibrous encapsulation. The severity of histologic injury, scored on a scale of 0-4 and quantitative analysis of the capsule wall thickness were determined for statistical analysis. Data were analyzed by Student *t*-test, one-way analysis of variance, Kruskal-Wallis or Mann-Whitney's tests as appropriate. A value of $P \leq 0.05$ was considered statistically significant.
Results: No behavioral changes or visible signs of physical impairment were observed at 8 days or 60 days post-implantation. Histopathologic observation of the implanted sites at each time-point showed that both Resilon and gutta-percha implants induced foreign body reaction, showing minimal to mild inflammatory reactions in most cases, which diminished significantly with time. Compared with gutta-percha, the capsule wall was thinner ($P > 0.05$) after Resilon implantation at day 8 and significantly ($P = 0.01$) thicker at day 60. In addition, capsule wall thickness showed a trend to increase with time after implantation in the Resilon groups ($P > 0.05$), opposed to the significant decrease ($P = 0.016$) observed after implantation in the gutta-percha groups, suggesting lesser long-term biocompatibility of Resilon.
Conclusion: Our findings validate Resilon as an *in vivo* biocompatible material. However, our data suggest that long-term biocompatibility of Resilon, despite validated, is inferior to that of gutta-percha control.

Key Words: Endodontic materials, gutta-percha, rat, Resilon, subcutaneous implantation

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Address for correspondence:
Dr. Miguel Cardoso,
Centro Médico de Tondela,
Rua Comandante João de Matos Ferreira, no 88,
3460-549 Tondela, Portugal.
E-mail: miguelbcardoso@gmail.com

INTRODUCTION

Proper selection of a biocompatible endodontic material is of paramount importance since biocompatibility may influence the long-term success of dental repair.

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Resilon, the core material of Resilon/Epiphany obturation system, was introduced in 2004[1] as a promising new endodontic material. It is the first obturation system to claim the ability to form a "monoblock" between the canal walls and obturation material.[2] Resilon is a polycaprolactone polymer that contains bioactive glass and radiopaque fillers. It was described as a thermoplastic, synthetic polymer-based root canal filling material,[1] which performs like gutta-percha. This latter has been the most widely used material in root canal obturation because of its well-known low toxicity and biocompatibility,[3,4] but it has drawbacks such as the lack of adhesion to

the canal walls.[3,5] Based on previous investigations, advantages of these new systems include a better biocompatibility than gutta-percha showed by a cytotoxicity study,[6] higher fracture resistance of teeth filled with Resilon compared with similar teeth filled with gutta-percha[5,7-9] and increased resistance to microbial leakage,[1,10-12] although controversial. Despite the growing evidence for Resilon's importance for endodontic treatment,[13] conflicting data regarding its biocompatibility has been emerging in *in vitro* studies.[6,14-22] Moreover, there are only few studies addressing Resilon's cones biocompatibility using an *in vivo* approach.[23,24]

The objective of this study was to investigate whether Resilon is biocompatible and characterize the histopathological effects of Resilon cones on subcutaneous connective tissue of rats for 8 days (short term) and 60 days (long term), comparing them with gutta-percha.

MATERIALS AND METHODS

Adult male Wistar rats (Charles River Laboratories, France), weighing 225-300 g, were used for the experiment. The animals were individually housed in a 12 h light/dark cycle with food and water available ad libitum. All procedures were in accordance with the standards of the National Institutes of Health as set forth in the Guide for the Care and Use of Laboratory Animals (National Research Council, Washington: National Academy Press, 1996). Approval for this study was obtained from the Faculty of Medicine of the University of Coimbra's Institutional Board and Ethics Committee.

Materials used in the study were: Resilon (#35; 0.06 taper Resilon cones-RealSeal Introductory Kit®, SybronEndo-USA, code 06B11) and gutta-percha cones (#35; 0.06 taper, Dentsply, Ballaigues).

Resilon (15 mm length, $n = 32$) or gutta-percha (15 mm, $n = 32$) points of sectioned cones were implanted subcutaneously in the backs of 16 rats for 8 days or 60 days. Two rats (one at each time-point) had unimplanted surgical sites and served as sham controls.

Briefly, the rats were anesthetized using intramuscular injection of ketamine (100 mg/kg)/chlorpromazine (5 mg/kg) before the beginning of surgery. After reaching a full level of anesthesia as assessed using tail pinch, each animal was placed in ventral decubitus position and the four quadrants of the back were shaved and prepped with iodopovidone. A small incision was made in each of the four dorsal quadrants of each animal and small subcutaneous pockets were developed deep inside the loose areolar tissue using blunt dissection. A previously sectioned cone of Resilon or gutta-percha was inserted into each pouch. Each rat was implanted with four pieces of the same material. The skin was closed using 4/0 non-absorbable sutures. The same surgical procedures were made in two rats, but the subcutaneous pockets were left empty. Following surgery, rats were returned to the animal facilities and remained there for either 8 days or 60 days.

At specific time-points (8 days or 60 days), rats were euthanized and weighed. The surgical sites were visually evaluated for signs of inflammation and material rejection. The implants and surrounding tissues were harvested and were fixed in 10% formalin solution. The explanted tissue was embedded in paraffin and sectioned using a microtome to about 4-5 μm thickness, and stained with hematoxylin and eosin and Masson's trichrome stain.

Samples were viewed using a light microscope and the presence of neutrophils, lymphocytes, macrophages, and giant cells were characterized as evidence of tissue response. The thickness of the inflammatory zone and collagen deposition were blindly assessed by two of the authors.

The severity of tissue injury was scored on a semi-quantitative scale from 0 to 4 under light microscopy where 0 indicates normal (absent reaction, i.e., no capsule or signs of inflammation visible on the sample), 1 indicates minimal changes (visible fibrous capsule involving the material without signs of inflammation or few inflammatory infiltrate), 2 indicates mild changes (fibrous capsule involving the material and presence of mild chronic inflammatory infiltrate, i.e., lymphocyte and/or plasmacyte infiltration), 3 indicates moderate reaction (fibrous capsule involving the material and intense infiltrate of macrophages and/or neutrophils, and/or foreign body giant cells) and 4 indicates marked reaction (tissue necrosis and substitution of connective tissue by an intense chronic inflammatory infiltrate), according to other classifications.[25,26] Tissues with persistent histological scores of 2 or higher were considered to have unacceptable biological response.[27]

In addition, capsule wall thickness was quantified for each specimen by image analysis using SigmaScan

Pro software (Version 5.0.0; Sigma, St. Louis, MO). Capsule wall thickness was expressed as a ratio, obtained by dividing the capsule wall area by the biomaterial area ($I_C/_B$); the higher the $I_C/_B$, the higher the thickness of the capsule wall. All measurements were performed on blind coded slices.

Statistical analyses were performed using SPSS Software Version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± standard error of the mean. Normality of distribution was determined using Kolmogorov-Smirnov test. Student *t* test, one-way analysis of variance, non-parametric Kruskal-Wallis test or Mann-Whitney U-test were used as appropriate. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

After surgery, all rats showed weight gain throughout the study and remained in good health. No acute inflammation, tissue necrosis, or abscess formation were observed around the implanted materials. At 8 days or 60 days after implantation, all implants remained *in situ* and surgical wounds were well cicatrized, showing no signs of infection or rejection (i.e., tissue necrosis, erythema). Upon inspection, all materials were grossly intact and the surrounding connective tissue showed no scars or calcification.

Tissue histology

Some specimens were lost during the histological processing, resulting in the following sample distribution according to the experimental periods: R-d8 (n = 12), G-d8 (n = 13), R-d60 (n = 15), G-d60 (n = 11), where R stands for Resilon, G stands for gutta-percha, d8 stands for day 8 and d60 stands for day 60.

Histopathologic observation of the implant sites at each time-point showed that both Resilon and gutta-percha implants induced foreign body reaction with the formation of a capsule while a minimal response was observed with a transitory thin inflammatory infiltrate without collagen deposition in unimplanted control tissues.

Tissue response for both implants at 8 days post-implantation [Figure 1a and b] consisted of a thin capsule, proliferating fibroblasts, mononuclear macrophages at the implant/tissue interface and no acute inflammation (neutrophils). Tissue response for both implants at 60 days post-implantation [Figure 2a and b] consisted of a more mature fibrous tissue capsule characterized by aligned extracellular collagen fibers embedded with spindly fibroblasts into their walls; moreover other infiltrating cells disappeared completely and once more, no signs of tissue toxicity, namely necrotic or calcifying areas, were observed.

Figure 3a-c presents the ranking of histologic tissue injury. At day 8 [Figure 3a] tissue injury was minimal

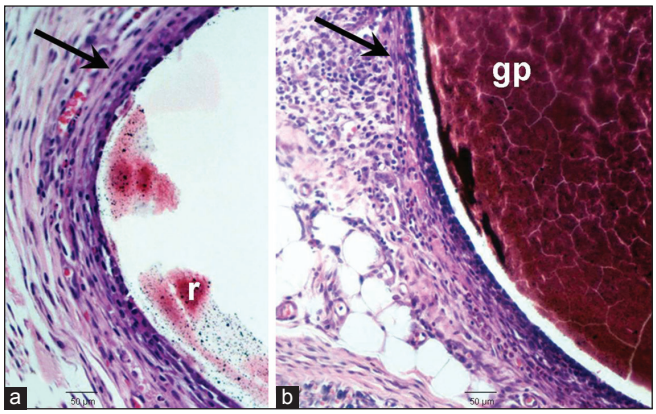

Figure 1: Light micrographs showing histologic lesions in subcutaneous tissue of rats implanted with Resilon or gutta-percha at day 8. H and E staining (scale bars=50 μm). R: Resilon; gp: Gutta-percha. Black arrows indicate tissue/material interface reactions

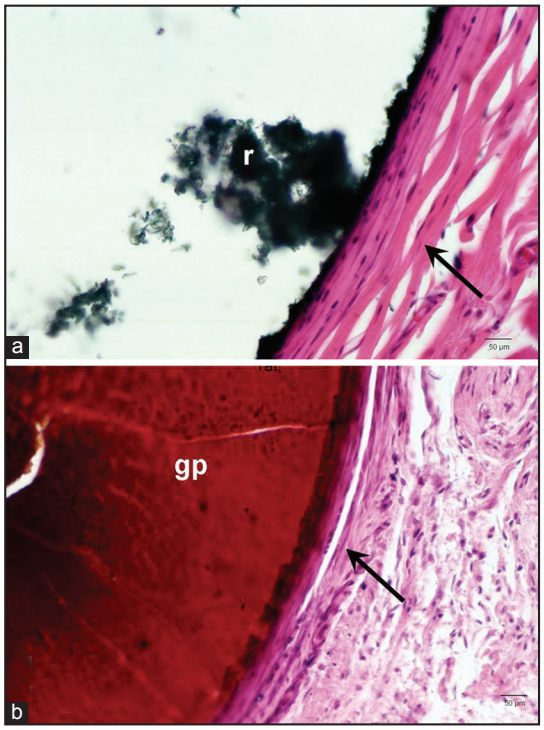

Figure 2: Light micrographs showing histologic lesions in subcutaneous tissue of rats implanted with Resilon or gutta-percha at day 60. H and E staining (scale bars=50 μm). R: Resilon; gp: Gutta-percha. Black arrows indicate tissue/material interface reactions

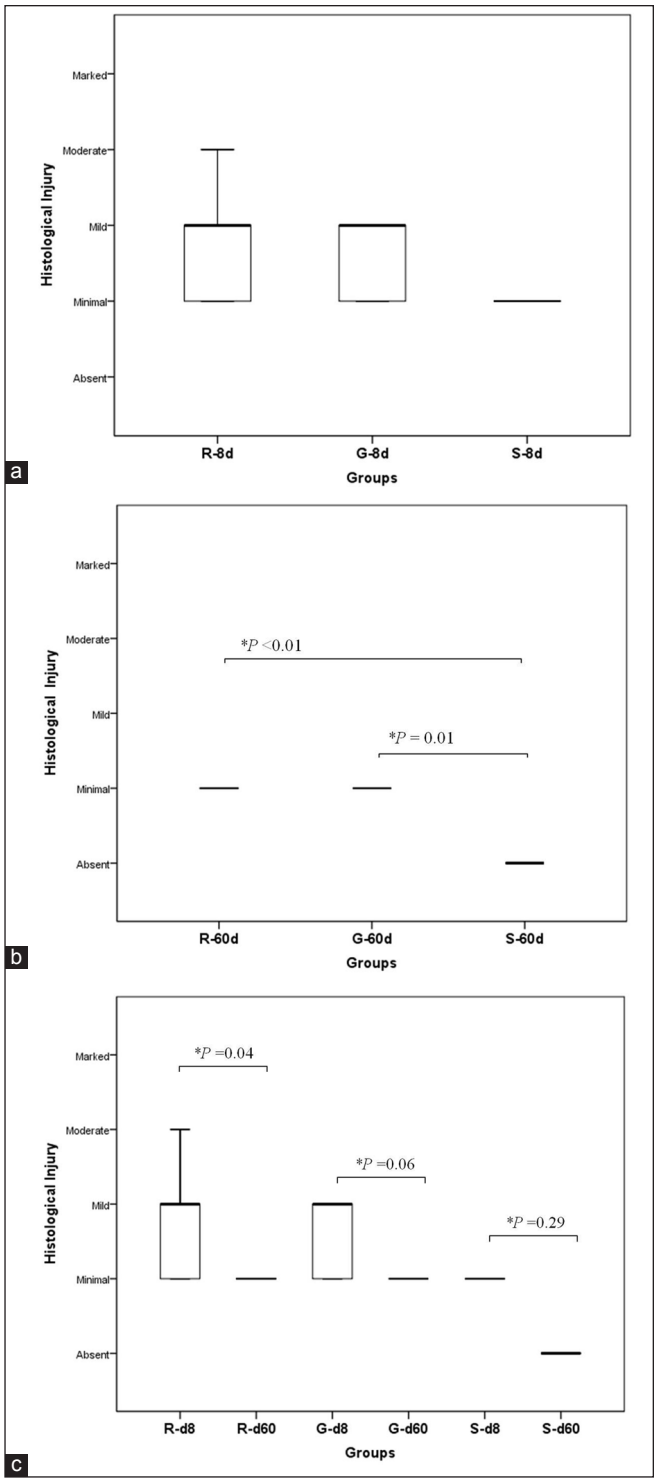

Figure 3: Comparison of histological injury grades among groups after implantation in rats. (a) Box-and-whisker plots representing injury grades at 8 days post-implantation; the central box represents the values from the lower to upper quartile (25-75 percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value. (b) Injury grades at 60 days (median values) post-implantation. (c) Represents injury grades progress from 8-day to 60-day in Resilon, Guta-percha and Sham groups. R: Resilon; gp: Gutta-percha; S: Sham; d8: Day 8; d60: Day 60; *P = significant

(score 1) or mild (score 2) in both Resilon (92%) or gutta-percha (100%) implant sites and minimal (score 1) in the sham control group ($P > 0.05$) and at day 60 it was minimal (score 1) at implant sites of Resilon or gutta-percha groups and minimal/absent in unimplanted site, showing a statistical significant difference among groups at this latter time-point (non-parametric Kruskal-Wallis, $P < 0.001$). Intergroup comparisons at day 60 showed similar tissue response of Resilon and gutta-percha groups ($P > 0.05$); however, a significant difference was achieved for pairwise comparison between the Resilon group and gutta-percha group versus the Sham group (R-60d vs. S-60d and G-60d vs. S-60d, $P < 0.01$ and $P = 0.01$, respectively), indicating a more favorable tissue response for the gutta-percha control group. Tissue injury progression with time showed that it subsided significantly in all groups [Figure 3c], indicating biocompatibility of both dental materials.

Capsule wall thickness measurement

Capsule wall thickening was quantified in Resilon and gutta-percha implants at both time-points [Figure 4]. Comparison between groups at day 8 post-implantation showed a trend for less thickness of the capsule in Resilon group than in the gutta-percha control (R-d8: 0.21 ± 0.029 vs. G-d8: 0.34 ± 0.059, $P = 0.067$); however without statistical significance, indicating a similar biological effect at this earlier time-point. Comparison between groups at day 60

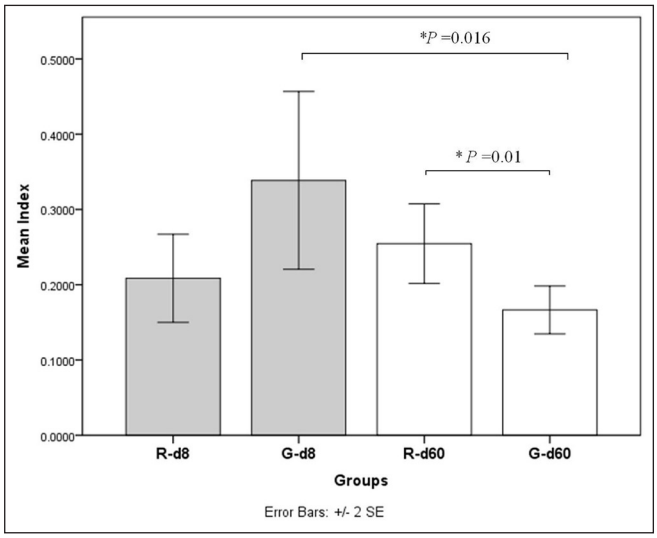

Figure 4: Comparison of capsule wall thickness between Resilon and gutta-percha groups after implantation in rats at 8 days or 60 days and over time. Values are mean±standard error of the mean. R: Resilon; GP: Gutta-percha; D8: Day 8; D60: Day 60; *P = Significant

post-implantation showed that the capsule wall was significantly thicker in the Resilon group compared to the gutta-percha control group (R-60d: 0.25 ± 0.026 vs. G-60d: 0.17 ± 0.015, $P = 0.01$), indicating less late biocompatibility of Resilon material. This was also identified by comparison of capsule wall thickness progression with time, which showed a slight thickening in the Resilon groups (day 8: 0.21 ± 0.029 vs. day 60: 0.25 ± 0.026, $P = 0.254$), opposed to the significant decrease observed in the gutta-percha groups (day 8: 0.34 ± 0.059 vs. day 60: 0.17 ± 0.015, $P = 0.016$).

DISCUSSION

The main goal of endodontic treatment is to provide a tight apical and coronal seal using biocompatible materials. A hermetic seal allows healing of the periapical tissue and prevents apical periodontitis and infection of the root canal.[11] Moreover, the root canal filling material should be compatible with the surrounding tissues, a fundamental property since materials can come in close contact with periapical tissues.

Gutta-percha is the most widely used material for root canal filling and despite its numerous favorable properties, like pure gutta-percha´s biocompatibility;[4] however, it has two major drawbacks: Poor sealing ability and inability to further strengthen the teeth,[3] Resilon is a recent advance in root canal filling materials. The significant improvement brought by Resilon, when compared to gutta-percha, is claimed to be its bonding to the dentinal walls when used in conjunction with its sealer, a dual-curable methacrylate resin sealer (epiphany). According to several authors, this combination results in a monoblock,[2] which mechanically increases the fracture resistance of instrumented roots.[7-9] In addition, Resilon provides a barrier that resists bacterial leakage[1,10-12] by creating a bond with dentinal walls[1,2] and allows the use of possible safer organic solvents during retreatment.[28] Because of its acclaimed superior characteristics Resilon has emerged as a promising alternative to gutta-percha.[29] However, others studies show different results.[30-34] Raina *et al*. found that there was no difference between gutta-percha/AH Plus and Resilon/epiphany and that a "monoblock" root filling, which did not leak was not created for either root canal filling[30] and concerning fracture resistance, Hanada *et al*. found that there was no significant improvement in resistance to vertical root fractures using Resilon compared with gutta-percha.[31] Furthermore, polymerization shrinkage,[35] poor marginal seal under higher pressure levels[36] and susceptibility to biodegradation[37,38] were considered as Resilon's disadvantages.

The understanding of the inflammatory response to filling materials is essential for their clinical success. Knowledge about this response might be beneficial in predicting potential complications associated with overextrusion of the material into the periapical tissue. As already known by other studies in the biocompatibility field, inflammatory response patterns induced by endodontic materials may be different in *in vitro* and *in vivo* studies.[39]

The objective of this study was to conduct an *in vivo* experiment to contribute to the understanding of biocompatibility of Resilon, comparing it with gutta-percha. A commonly used method to assess biocompatibility is the subcutaneous implantation of the material to be studied in small animals. Histopathological effects of Resilon cones on subcutaneous connective tissue of rats were compared with gutta-percha's at 8 days (short term) and 60 days (long-term) following implantation. Both time points have been traditionally used in the majority of *in vivo* studies accessing material biocompatibility: The 1st time point was used to detect acute adverse reactions and the 2nd time point to detect later injuries.[23,24,39,40]

Taken together, data from this study support the *in vivo* biocompatibility of Resilon. Firstly, it was shown that Resilon was non-toxic as demonstrated by the presence of grossly normal subcutaneous surrounding tissue and normal behaving animals, which consistently gained weight, similarly to the controls. Secondly, tissue response was mostly minimal or mild and diminished significantly with time, which conforms with the recommendations of the "Federation Dentaire International" for accepting dental materials as biocompatible.[41] Finally, our findings are in agreement with other studies, which have confirmed this favorable tissue response.[23,24] Using Resilon or gutta-percha cones implanted into the dorsal connective tissue of rats, Onay *et al*.[23] have shown that both materials induced a moderate to severe inflammatory reaction at the 1-week time point, which decreased at the 8-week observation time point and Bodrumlu *et al*.[24] have shown that Resilon or gutta-percha cones exhibited less inflammation

after the first post-operative week, which subsided by the 60th day.

However, in the present study, quantitative measurement of the implant capsules, at 60 days and over time, suggests that long-term biocompatibility of Resilon, despite validated, is inferior to gutta-percha control. Noticeably, at day 60 a thicker encapsulation of Resilon was found compared to gutta-percha control. Moreover, a different encapsulation progression was found: While the thickness of gutta-percha capsule diminished over time that of Resilon did not. This latter result is not consistent with the study of Bodrumlu *et al*.[24] in which the opposite occurred, that is the thickness of the capsule decreased over time after Resilon implantation and increased with gutta-percha. These differences may be explained by the different methods used to measure the thickness of the capsule. We believe our data represents a more accurate result since the calculation of the $I_C/_B$ is more precise than the simple measurement of the capsule thickness described in that report.[24] Measuring $I_C/_B$ excludes the bias induced by the amount of material eliciting tissue injury, which varies with the diameter of the cone at the site of histological cut. Therefore, direct thickness of the capsule is only comparable if this site of cut is precisely the same in all cones, contrarily to the $I_C/_{B,}$ which eliminates this error factor.

The exact mechanism for the non-decrease of the Resilon encapsulation over time remains unclear. One may postulate that the degradation of this material by the action of organic fluids, with continuous irritation by the released by-products, may play a role, even though we only found one case of foreign body granuloma in histologic staining. In keeping with this assumption, Tay *et al*.[37,38] found that Resilon is susceptible to degradation by alkaline and enzymatic hydrolysis and exhibited extensive surface thinning and weight loss after incubation in hydrolytic enzymes. The biodegradation of polycaprolactone probably exposes the polymer matrix, a phenomenon that increases over time. In gutta-percha specimens, only superficial pores were created by enzymes, with no further degradation changes.[38] In addition, several studies have shown short-term moderate to severe cytotoxicity of Resilon[14,16,18] and another study reported that both commercially available core materials (gutta-percha and Resilon) were severely cytotoxic over an extended (6 week) testing period.[19] Initial and long-term cytotoxicity likely stems from potential elution of monomers from the resin matrices, as already suggested for several dental materials.[18,20,38,42]

Overall, our findings validate Resilon as an *in vivo* biocompatible material. However, our data suggest that long-term biocompatibility of Resilon, despite validated, is inferior to gutta-percha control.

Further research is necessary to complement these results in longer observational periods and to understand its clinical significance.

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