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Title:
Comparison of ACTIVA™ BioACTIVE versus Compomer for class II restorations in primary molars: A split mouth randomized controlled trial

Original Article

This master thesis is submitted for obtaining a master's degree in the direction of Master of Science in Advanced Dentistry – Pediatric dentistry and Special care

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1. List of abbreviations

ASA	American society of Anesthesiologists
BisGMA	bisGlycidyl ether diMethAcrylate
BMP	Bone Morphogenic Proteins
CONSORT	CONsolidated Standards Of Reporting Trials
DMFT	Decayed Missing Filled Teeth (Permanent teeth)
dmft	Decayed Missing Filled Teeth (Deciduous teeth)
F	Fluoride
FDA	Food and Drug Administration
FTIR	Fourier-Transform InfraRed spectroscopy
GIC	Glass Ionomer Cement
HAp	hydroxyapatite
LoE	Level of Evidence
MTA	Mineral Trioxide Aggregate
PAMC	Polyacid Modified Composite
PI	Plaque index
RBC	Resin Based Composite
RCT	Randomized controlled trial
RMGI	Resin Modified Glass Ionomer
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
TEGDMA	TriEthylene Glycol DiMethacrylate
TGF-β_1	Transforming Growth Factor
USPH	United States Public Health Service

2. Abstract

Introduction: ACTIVA™ BioACTIVE (Pulpdent®) is a recently developed ionic resin material with bioactive properties. It is able to release and recharge calcium, phosphate and fluoride ions.

Aim: The aim was to evaluate ACTIVA™ BioACTIVE in class-II restorations in primary molars compared with a Compomer (Dyract®) (Dentsply).

Methods: Using a prospective double-blind split mouth design, a total of 80 restorations (ACTIVA™=40, Dyract®=40) were placed randomly in twenty children aged 5-10 years (mean age: 7.3 yrs.) by one operator. Pre-operative plaque index (PI), DMFT/dmft scores and the time taken to place the material were recorded. After 6 months, the teeth were evaluated clinically and radiographically by two calibrated and blinded examiners using U.S. Public Health Service Ryge Criteria. Both scores "A and B" were combined and considered as "success". Score "C" was considered as "failure". McNemar and paired student's *t*-tests were used for statistical analysis.

Results: The mean PI was 1.48, while the mean DMFT/dmft score was 0.35 and 6.55 respectively. After 6 months follow-up, no statistically significant difference was found between the success rate of ACTIVA™ (100%) and Dyract® (95%). There was no significant difference between both materials with respect to color match, marginal discoloration/adaptation, anatomic form, tooth/restoration fracture and secondary caries; while the mean time taken to place ACTIVA™ was significantly less than Dyract® ($P < 0.001$).

Conclusion: After 6 months follow-up, both materials had an excellent clinical performance in class-II cavities in primary molars in children with high caries experience. However, ACTIVA™ took significantly less time to be placed. Longer follow-up evaluation is needed to validate the success rate of this bioactive filling material.

3. Introduction

Many efforts have been invested in order to produce the most suitable dental restorative material. Many types of material are fabricated for different dental purposes (1).

A cavity in a tooth should be restored with proper filling material that bears the occlusal force and withstand the acidic and bacterial attack and survive in the oral environment in addition to be biocompatible with the oral tissue. In the past, Amalgam was widely used as a restorative material, but its usage decreased due to its inferior aesthetic, inability to adhere to tooth structure and environmental reasons (2).

The amalgam was replaced by tooth colored restorations including glass ionomer cements (GIC), resin modified glass ionomers (RMGI), polyacid modified composites (PAMC) and resin based composites (RBC), which have superior esthetic properties and require less removal of tooth structure (3, 4).

3.1 Polyacid modified composite (PAMC)

Polyacid-modified composite resins (PAMC), known as Compomers, are a group of aesthetic restorative materials. They were introduced to the dentistry in the early 1990s (5), and were developed as a new class of dental material designed to combine the aesthetics of Resin Based Composite (RBC) with the fluoride release of Glass Ionomer Cement (GIC).

PAMC material possesses only a photochemical polymerization reaction in the setting reaction. An acid-base reaction occurs only after the sitting upon absorption of water from the surrounding. As such, these materials cannot be considered as GIC. PAMC materials differ from GIC in at least two aspects; the first aspect is that glass particles are partially silanized to provide a direct bond with the resin matrix, and second is that the matrix is formed during the light activated radical polymerization reaction of monomers (6).

A key feature of PAMC is that they contain no water and the majority of components are the same as for composite resins, mainly bulky macro-monomers, such as bisglycidyl ether dimethacrylate (bisGMA) or urethane dimethacrylate, which are combined with viscosity-reducing diluents, such as triethylene glycol dimethacrylate (TEGDMA). These polymer systems are filled with non-reactive inorganic filer, such as quartz or a silicate glass. These

fillers are coated with a silane to promote bonding between the filler and the resin matrix in the set material (7, 8).

Polymerization in PAMC is associated with a contraction stress, as it is in conventional RBC, as rapid development and high value of contraction force could be a possible cause of failure of the bond to the tooth, but Dyract® PAMC might prove superior in maintaining a proper bond with the cavity walls because of its lower polymerization stress (9).

PAMC is widely accepted as a standard restorative material for primary dentition for Class I and II cavities. The range of success rate of PAMC in Class II restorations in primary molars is 78-96% (average 87%) (10-23). The risk of developing secondary caries and failure In Class II Compomer restorations in primary teeth didn't increase over a period of two years follow-up. Many randomized clinical trials have reported comparable clinical performance to RBC with respect to color matching, marginal discoloration, anatomical form, marginal integrity and secondary caries. In comparison to GIC and RMGI, PAMC tend to have better physical properties in the primary dentition. However, the cariostatic properties of PAMC didn't differ significantly from those materials (24).

In contrary to the conventional GIC, PAMC lack the ability to bond chemically to tooth structure. Therefore, bonding of PAMC to the calcified tooth structure depends on the use of a prime/bond system which is preceded by etching the tooth structure. PAMCs are able to release fluoride ions. However, the amount of released ions is significantly lower than those of GIC. Such low levels of fluoride ion release have been shown to jeopardize the degree of protection afforded by these materials (6, 25).

3.2 The role of Fluoride in dentistry

Fluoride (F) is the key element to understand contemporary fluoride-contained restorative materials. The role of F in preventing dental caries has been well-documented. It is a well understood fact that F ions have an anti-cariogenic property and it prevents initiation and progression of caries by forming a caries resistant complex with the inorganic portion of tooth structure. Such a benefit arises from both systemic and topical application of F. Those ions can be delivered to the oral environment by several means: either at home through fluoridated dentifrice, mouthwash and diet, or professionally by the dentist through varnishes, pit & fissure sealants or fluoride realizing dental materials. Various factors govern

F release from restorative materials e.g. composition, powder liquid ratio, setting reaction and F content of the material (26).

At the tooth-restoration interface, F is released from the restoration and taken up by tooth substrate, and subsequently strengthens the dentin. This function prevents microleakage and secondary caries and assists in the remineralization of decalcified enamel and dentin. Therefore, dental restorative materials which contain F in their formulation and able to provide sustained release of F might prove to be helpful in the inhibition of secondary caries in the restored tooth as well as dental caries in the adjacent teeth (27).

3.3 Bioactivity & Biocompatibility

There is a wide confusion between the concept of biocompatibility and bioactivity. In 1986, the consensus of a U.K. conference gave biocompatibility a proper definition as "the ability of a material to perform with an appropriate host response in a specific application" (28). Williams also defined the biocompatibility as "The ability of a biomaterial to perform its desired function, without eliciting any undesirable local or systemic effects in the recipient" (29). Meaning that a material can be biocompatible as long as it causes no side effects to the recipient like most of the above mentioned dental materials.

A bioactive material on the other hand can be defined as "a material that undergoes specific surface reaction when implanted into the body, integrating with the body and forming a layer of material inherent to the body, for example hydroxyapatite (HAp), this layer is responsible for the formation of a firm bond with hard and soft tissues" (30). The integration of the bioactive material with the hard tissue occurs due to solubilisation of proteins, such as growth factors like Transforming Growth Factor TGF-β_1, from the exposed bone, and due to bone morphogenic proteins (BMP) and collagen that can bind easily with the HAp layer. An example of such behaving bioactive materials is bioactive glass and synthetic HAp (31, 32).

On the tooth level, the solubilisation of growth factors from the dentine as a reaction to a bioactive material may cause modulation in odontoblast-like cells with subsequent natural healing of the tooth, either by stimulation of resident cells to deposit new mineral through the process of reactionary dentinogenesis, or by stimulation of cells to differentiate into odontoblast-like cells which produce new mineral through reparative dentinogenesis (33). A good example for this kind of bioactive materials is some pulp-capping materials like:

calcium hydroxide, calcium based materials, Portland cement, Mineral Trioxide Aggregate (MTA), Biodentine and Bioaggregate (34, 35).

Based on this concept, GICs, RMGIs and conventional RBC probably are not bioactive as they release or take up very low amount of Ca^{2+} and PO_4^{3-} (36, 37).

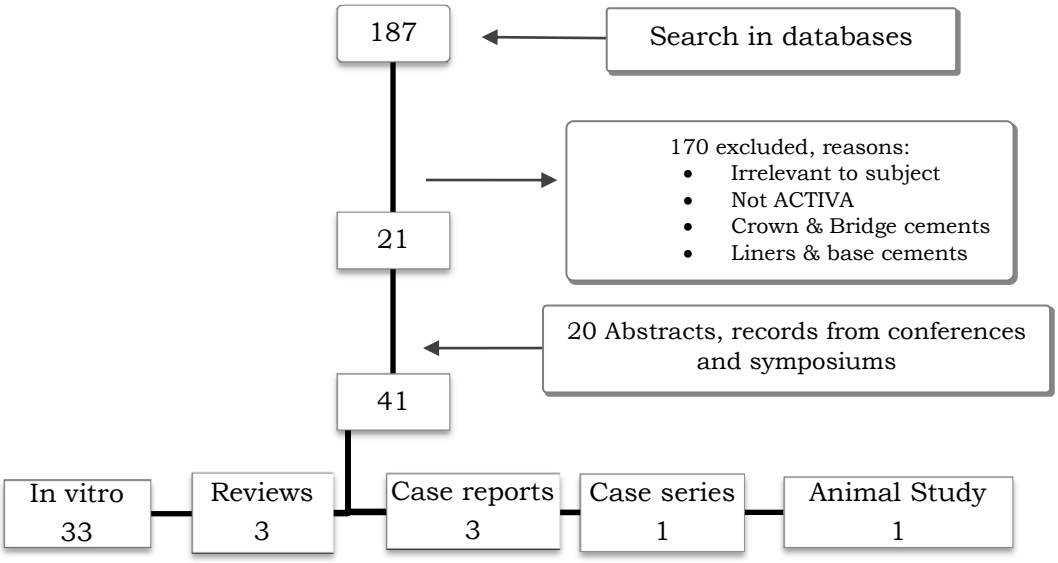
In 2013 Pulpdent® Corporation acquired the premarket approval from the US Food and Drug Administration (FDA) to introduce new bioactive restorative materials in attempt to overcome the disadvantages of GIC and RBC and combine their advantages in one restorative material, namely ACTIVA BioACTIVE™ (Pulpdent MA, USA) (38).

4. Review of the literature regarding ACTIVA BioACTIVE™

An electronic search was conducted in several databases: Medline (PubMed), Web of Science, Google Scholar and Embase in order to review the available information in the literature regarding ACTIVA BioACTIVE™ materials. Further search was done in ClinicalTrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) to include any registered completed or ongoing clinical trials. All abstracts and records from conferences, sessions, symposiums or meetings were reviewed.

Search terms were: ACTIVA BioACTIVE, dental material, restorative, bioactive material.

All articles were then reviewed and included based on the title, abstract or the full text. All articles related to endodontic materials, implants or crown & bridges were excluded.



Flow chart 1: Search methodology

The search ended up with 41 articles: thirty three *in vitro*, three narrative reviews about bioactive dental restorative materials, two case reports, one case series and one animal study. There were neither completed and published nor ongoing clinical trials (Table 11).

The Oxford Centre for Evidence-based Medicine instrument 2011 was used to determine the Level of Evidence (LoE) (39) (see further 4.11).

4.1 ACTIVA BioACTIVE™

Those materials are ionic composite resins which combine the biocompatibility, chemical bond and the ability to release fluoride of GIC with the mechanical properties, aesthetic and durability of RBC. In addition to that, it is claimed that those materials have bioactive properties as the US Food & Drug Administration has allowed the claim that ACTIVA BioACTIVE products contain a bioactive matrix and bioactive fillers which make them distinct from other mentioned tooth colored restorative materials (38, 40).

ACTIVA BioACTIVE materials are:

- ACTIVA BioACTIVE Base/Liner: placed in deep cavities as a base layer under the bulk filling to protect the pulp. It is 45% filled by weight, has a lower pH than the Restorative. It is dentin shade and is dispensed by hand with a standard plunger type syringe.

- ACTIVA BioACTIVE Cement: used for cementation of crown and bridges.

- ACTIVA BioACTIVE restorative: Used as permanent restoration in both primary and permanent dentition. It is 56% filled by weight, more viscous, and provides slightly greater strength and wear resistance in comparison to Base/Liner. It is available in A1, A2, A3, and A3.5 shades and applied using a dispenser.

- ACTIVA Kids BioACTIVE restorative: It has similar features as ACTIVA restorative, the only difference is that It has an opaque white shade to mimic the shade of primary dentition (40, 41).

In this review, only ACTIVA BioACTIVE restorative will be discussed in details.

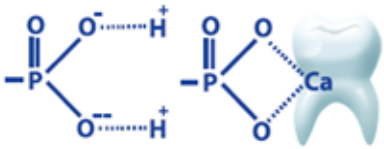
4.2 ACTIVA BioACTIVE restorative, is it GIC or RBC?

The nature of ACTIVA is a perplexing issue as there is contradiction in the literature about the right category of this material whether it is RMGI or RBC.

It is known that GIC materials require a chemical reaction to initiate a setting reaction (42), while the setting reaction of light cured-RBC can be induced by light (43). Therefore, the more the filling material sets by a chemical reaction e.g. RMGI, the more GIC it is; and the more the filling material sets by photoreaction e.g. PAMC the more RBC it is (Figure 1).

ACTIVA is a two-paste system in automix syringe and has a triple cure reaction, light cure reaction, self-cure resin reaction and self-cure glass ionomer reaction (40). The material can set only with a chemical reaction, but the light cure will help to increase crosslinking polymers and enhance the physical properties.

If we would apply this concept then ACTIVA can be considered as RMGI as reported by several articles (44-46) as it contains 2 acids, while other articles referred it as ionic resin composite (47-51) due to the fact that the chemical cure is not only a GI reaction but also combined with the self-cure resin composite. Furthermore, the manufacturer claims that Fourier-transform infrared spectroscopy (FTIR) technology shows that it is not a strictly a RMGI. The description "ionic" was based on ionization process of the phosphate group between the resin and glass filler at one side and the tooth structure on the other side, as the hydrogen ions break off from the phosphate groups and are replaced by calcium in tooth structure, forming an ionic bond between the filling and the tooth structure, according to the manufacturer (40).



The material contains also a bioactive filler which makes it bioactive and able to form a hydroxyapatite layer (52), so if we would describe the material based on those facts it would be "Resin-modifies Glass-ionomer bioactive ionic resin-based composite", or simply "ionic bioactive resin material".

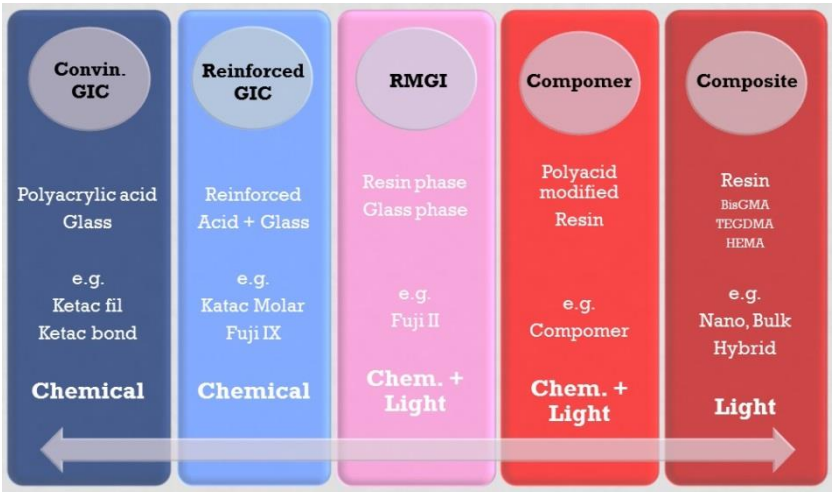


Figure 1: Categories of restorative materials

4.3 Physical properties

ACTIVA was compared to several restorative materials, RBCs and GICs regarding different physical properties. ACTIVA had compressive and diametric tensile strength comparable to Filtek Supreme Ultra and higher than Ketak Nano and Fuji IX (53). The flexural strength and flexural fatigue were lower than Filtek Supreme Ultra but comparable to Tetric EvoFlow and Beautifil Flow Plus, and higher than other RMGIs and GICs (45, 53).

Table 1: Physical properties of ACTIVA restorative and liner (54)

PHYSICAL PROPERTIES	RESTORATIVE	BASE/LINER
Light cure setting time:	20 seconds	20 seconds
Depth of light cure:	4 mm	4 mm
Initial self-cure setting time at 37° C:	2½-3 minutes	2½-3 minutes
Percentage filler by weight:	56%	45%
Percentage reactive glass filler by weight:	21.8%	19.3%
Fluoride release 1 day:	230 ppm	360 ppm
Fluoride release 28 days (cumulative):	940 ppm	1,300 ppm
Flexural strength:	102 MPa/14,790 Psi	86 MPa /12,470 Psi
Flexural modulus:	4.3 GPa	3.7 GPa
Compressive strength:	280 MPa /40,600 Psi	226 MPa /32,770 Psi
Diametral tensile strength:	42 MPa /6090 Psi	37 MPa / 5365 Psi
Water sorption (1 week):	1.65%	2.30%
Polymerization shrinkage:	1.7%	N/A
Film thickness:	N/A	11 microns

ACTIVA showed significant greater deflection at break in comparison to Ketac Nano and Fuji IX, which may indicate better resistance to fracture which is reflected in higher flexural strength and the elastic modulus compared to the other materials (55).

4.4 Water absorption and solubility

ACTIVA is able to absorb an amount of water high enough to unlock the bioactive properties, but low enough not to jeopardize the physical properties (40).

ACTIVA and Filtek Supreme composite had a comparable water absorption and solubility which were significantly lower than other RMGIs and GICs (40, 48).

4.5 Fluoride release and reuptake

ACTIVA possesses the ability to recharge F from the oral cavity by means of fluoridated toothpaste or mouthwash and acting as a reservoir. When the level of F decreases and the PH drops in the oral cavity the material starts to release F. when the person brush his teeth with fluoridated dentifrice the material takes up F again and recharge it. This ability seems more important than only releasing F in high amount.

ACTIVA can maintain constant release of F (0.2 - 0.6 mg/L) over 21 days without recharging, which is higher than Filtek supreme (0.03 – 0.08 mg/L) and lower than Ketac Fil (2.1 – 3.5 mg/L) and Equia Forte (9 – 3.8 mg/L) (56).

Comparing ACTIVA to other GICs, ACTIVA releases lower amount of F than Fuji XI in artificial saliva at day 15, but after recharging using 5% sodium fluoride varnish, ACTIVA releases significantly higher F at 24 hours, 1 week and 3 weeks compared to Ketac™ Nano (RMGI) and Fuji Triage (GIC) (46, 57).

ACTIVA can also release F through bonding agents e.g. DenTASTIC™ UNO™ bonding (Pulpdent). The amount of released F is significantly lower if the material is covered with Clearfill™ SE or Scotchbond™ UNIVERSAL bonding agents (58).

4.6 Phosphate release

ACTIVA releases certain amount of Phosphate especially in low pH environment. The cumulative amount of Phosphate release from ACTIVA in 7 days period is around 300 mcg/g in pH 4, and 100 mcg/g in pH 7, indicating that ACTIVA exhibits different behavior according to the acidity of the environment (47).

4.7 Calcium release

ACTIVA has the ability to release calcium ions of an amount of 0.72 $\mu g/mm^2$. However, this amount is less than that released from Dycal (4.88 $\mu g/mm^2$) and TheraCal 9.12 $\mu g/mm^2$ in a period of 7 days (59). When comopared to Filtek Supreme, Ketac Fil and Equia Forte, ACTIVA released the highest amount of Ca^{2+} over 21 days (56).

4.8 Bioactive properties

Pulpdent claims that ACTIVA stimulates mineral apatite formation as the US Food & Drug Administration has allowed the claim that ACTIVA BioActive products contain a bioactive resin matrix and bioactive fillers, but there is no decisive evidence to prove this pretension (38, 40).

Formation of HAp was noticed on ACTIVA by field scanning electron microscope (SEM) imaging, PulseTor SDD (Silicon Drift Detector) and Energy-dispersive X-ray spectroscopy (EDS) analysis after immersion in phosphate-buffered saline (PBS) up to 30 days (Figure 2) (60). It has been also shown that ACTIVA has produced resin tags integrating into dentinal tubules. Ca/P ratio ranged from 2.0-2.5 across dentin, tags, and resin (52).

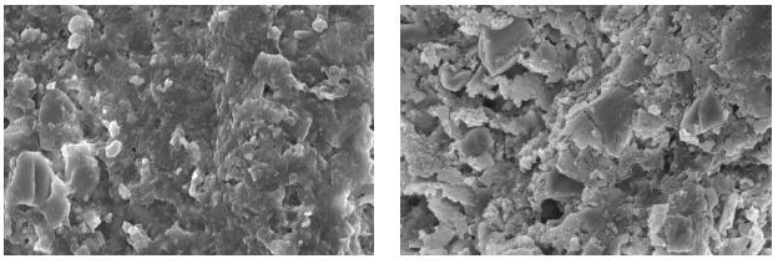


Figure 2: Surface Deposition Analysis of ACTIVA (60)

4.9 Wear resistance

ACTIVA has a surface wear against natural enamel comparable to Tetric Evo Ceram and Filtek Supreme Ultra, and significantly lower than Fuji IX (61). When the material brushed with a toothpaste, ACTIVA showed comparable wear resistance to Beautiful flow plus and Tetric Evo Flow using non-abrasive toothpaste and greater wear resistance than those two materials using abrasive toothpaste (62).

4.10 Radiopacity

The radiopacity of ACTIVA is equivalent to 1.5mm of aluminum (40).

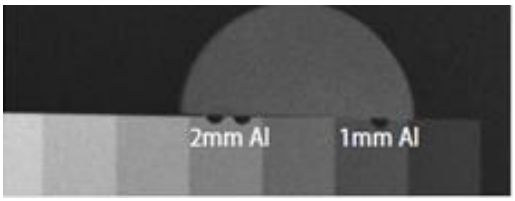


Figure 3: Radiopacity of ACTIVA

4.11 Level of Evidence

All included articles in this review were either *in vitro* studies (N=33), reviews (N=3), case reports (N=3), case series (N=1) or Animal study (N=1), indicating low level of evidence about the available information about the properties of this material. Currently there are no clinical trials or longitudinal studies *in vivo* to draw a definitive conclusion about the efficacy and long term success rate of the studied material. More standardized, well conducted and *in vivo* studies with long term evaluation has to be performed in order to address the treatment outcomes of ACTIVA BioACTIVE restorative material.

5. Aim and objectives

5.1 Aim

The aim of the study was formulated in a PICO question as follows:

In children with class II cavities in vital primary molars (P), does restoration with ACTIVA™ BioACTIVE (Pulpdent MA, USA) (I) in comparison to restoration with Compomer (Dyract® eXtra DENTSPLY, Germany) (C) result in similar or better clinical and radiographic outcomes (O) ?

5.2 Objectives

The primary outcome is to evaluate the clinical and radiographic outcomes of class II restorations performed on human vital primary molars using a new bioactive ionic resin material (ACTIVA™ BioACTIVE), while using the Compomer (Dyract®) as a control group.

The secondary outcome is to investigate whether both material take the same amount of time to be placed in the oral cavity.

Null hypothesis (H_0)

There is no difference between using ACTIVA™ and Dyract® in children to restore Class II cavities in carious vital primary molars.

6. Materials and Methods

6.1 Study design

An experimental prospective double blinded split-mouth randomized controlled trial (RCT) design was applied and reported according to CONSORT statement (CONsolidated Standards Of Reporting Trials) (63). The study was monocenter and was conducted in the department of Pediatric dentistry and special care, Ghent University Hospital, Belgium.

6.2 Sample size calculation

In order to calculate the sample size, several parameters were considered. The type one error was set at 5% (α=0.05), the power was considered as 80% with 95% confidence interval (CI) and the success rate of both materials was calculated.

The success rate of Dyract was estimated based on the literature. Twelve clinical studies with the same methodology as this study were included to calculate the success percentage. Other studies were not included because they either used FDI evaluation criteria (64), which is different from the criteria used in this study, or they combined class I and II cavities without reporting the success of class II restorations separately (65, 66).

The range of success rate of Dyract in Class II restorations in primary molars based on the twelve clinical studies was 78-96% (average 87%) (Table 2). One Meta-analysis reported 87% success rate (20), which was in accordance with the calculated average percentage from the twelve studies.

Regarding the success rate of ACTIVA, there were no clinical studies available in the literature that reported the clinical success percentage.

Therefore, a pilot clinical study was conducted to determine the success rate of ACTIVA. 20 teeth with class II cavities in vital primary molars were restored using ACTIVA. After 6 months evaluation, one tooth failed because of gross restoration fracture indicating a success rate of 95%.

The sample size was calculated based on the assumption of binary outcome measures (success/failure) using sealedenvelope™ calculator (Sealed Envelope Ltd. 2012). As the Dyract was the positive control group, the inferiority limit was set at 87%, and the non-

inferiority limit was fixed at 9%, as the success percentage ranged between 78-96% which was clinically acceptable.

Using the above mentioned parameters, a total number of 70 teeth (35 teeth per group) was required to detect a significant difference for a two sided type I error 5% and power of 80%. This number was increased to 39 teeth per group to allow for a drop-out rate of 10%.

Table 2: Articles reported Success rate of Dyract with level of evidence (LoE)

Author	Year	Type	Follow-up years	Number of teeth	Success rate %	LoE
Andersson-Wenckert I.E. (10)	1997	Clinical trial	2	104	78	3
Hse K.M. (11)	1997	Split mouth	1	21	95	2
Roeters J.J. (12)	1998	Clinical trial	3	37	89	3
Marks L.A.M. (13)	1999	Split mouth	3	17	94	2
Papagiannoulis L. (14)	1999	Clinical trial	2	68	90	3
Attin T. (15)	2000	Split mouth	2	64	89	2
Attin T. (16)	2001	Split mouth	3	46	79	2
Gross L. C. (17)	2001	RCT	2	26	96	2
Duggal M.S. (18)	2002	Split mouth	2	60	71	2
Qvist V. (19)	2004	RCT	7	374	85	2
Toh S. L. (20)	2007	Meta-analysis	1-3	596	87	1
Ertugrul F. (21)	2010	Split mouth	2	98	95	2
Ghaderi F. (22)	2015	Split mouth	2	14	85	2
Chisini L.A. (23)	2018	Systematic review	1-4	1723	91	1

6.3 Ethical committee & informed consent

After reviewing the study protocol by the ethical committee of Ghent University hospital, Ghent, Belgium under project number: EC UZG 2016/1050 & 2016/1051 according to the ICH good clinical practice regulations, an approval was given on 22/12/2016 under the Belgian registration number: B670201629533 & B670201629534.

The parents of all included patients received an oral explanation and detailed information letter about the treatment procedure and were asked to sign an informed consent after their

approval to participate in the study. A movie ticket and a parking ticket were provided for each patient in the follow up visits as remuneration.

The trial was registered in ClinicalTrials.gov under identifier number: NCT03516838.

6.4 Inclusion and exclusion criteria

6.4.1 Patient inclusion criteria

All included participants were healthy with ASA I score (American society of Anesthesiologists) from both genders and treated in the dental chair in the department of pediatric dentistry and special care, Ghent University hospital, Belgium. Only cooperative children aged between three to ten years with at least one carious vital primary molar on each side (split mouth) were recruited. All parents approved to participate in the study and signed the informed consent.

6.4.2 Tooth inclusion criteria

All included teeth were evaluated clinically and radiographically beforehand to determine the eligibility of each tooth.

The selected teeth were from both sides, both jaws (upper & lower) and both primary molars (first and/or second) with proximal enamel/dentine caries not more than a clinical ICDAS score of five. All included teeth should be vital, restorable and free of symptoms i.e. spontaneous pain, swelling, infection, fistula, abscess or tenderness on percussion. No extensive caries, dental developmental disturbance, pathological mobility, pulp exposure or indication for pulp therapy.

Radiographically, the teeth were chosen based on a pre-operative digital radiograph with proximal enamel/dentine caries confined to the outer half of the dentine with no endodontic involvement with predicted survival of at least 2 years until normal exfoliation.

If one or more of the above mentioned criteria is not fulfilled, the patient and/or tooth are excluded from the study.

6.5 Oral hygiene status

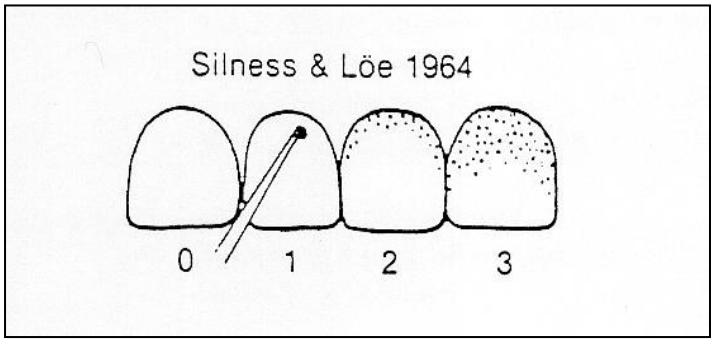
Two pre-operative dental indices were used to evaluate the oral hygiene status:

6.5.1 Plaque index by Silness and Löe 1964

The presence and the amount of plaque were assessed based on six teeth [16(55), 12(52), 24(64), 36(75), 32(72) and 44(84)] according to the criteria of Silness and Löe 1964 (67) (Table 3).

Table 3: The plaque index system by Silness and Löe

Scores	Criteria
0	No plaque after gentle probing
1	Plaque present after probing
2	Visual plaque < 1/3 of tooth
3	Visual plaque > 1/3 of tooth



Each surface received a score (0 to 3). All scores were totaled and divided by the number of scored teeth to determine the final index. The interpretation was as follows:

Good = 0.0-0.6

Fair = 0.7-1.8

Poor = 1.9 -3.0

6.5.2 Dental caries index (DMFT/dmft)

DMFT & dmft scores by Klein, Palmer and Knutson 1938 (68) for permanent and primary teeth were estimated with the following rules:

- Tooth counted only once.
- D, M and F scores are recorded separately.
- Decay + filling in the same tooth = D
- Many restorations are counted as one filling.
- DMFT and dmft scores are done separately and never added, permanent then primary.

6.6 Randomization and blinding

After applying the inclusion and exclusion criteria, the teeth were assigned randomly into two groups (ACTIVA™ or Dyract®) based on randomized sequences generated by the computer using Random Integer Generator (RANDOM.ORG, Randomness and Integrity Services Ltd.). The randomization was at the tooth level and not at the patient level, and the allocation ratio was set to be equal.

During treatment, the type of material was concealed from the patient, and the patient had no information which material was used in each side of the mouth. The type of restoration was not mentioned in the patient's file. Instead, it was replaced by a combination which the evaluators were not familiar with. The operator was also blinded for the type of restoration during tooth preparation and was informed only at the time of restoration placement. The purpose of this discretion was to ensure double blinding both at the patient, as well as the evaluators level.

6.7 Clinical procedure

All included children were treated in the dental chair by one pre-trained operator (master student) to avoid inter-operator bias. A pre-operative radiograph (bitewing) was taken for diagnosis. The tooth was anesthetized using local anesthesia, and isolated using rubber dam. Caries was removed using a high speed diamond pear (long head) bur (ISO 806 314 234 524) with or without round bur with ample water spray. Low speed hand piece or hand excavator was used to remove further deeper caries.

The proximal box was prepared with respect to the following dimensions:

- The bucco-lingual dimension occupies the middle third of the intercuspal span of the occlusal surface of the tooth.
- The buccal and lingual outlines of the box are parallel to the buccal and lingual surfaces of the tooth respectively.
- The gingival floor should exceed the contact point and shouldn't reach the cement-enamel junction.
- The axial wall should be perpendicular to the gingival floor.
- The cavo-surface margin of the axial wall should be parallel to the proximal surface of the tooth.
- The cavo-surface margin is not beveled.

After caries removal, a metal matrix band (V3 Sectional Matrix System™) was fixed around the tooth to form the proximal wall of the restoration, and a wedge was placed interdentally to preserve the gingival interproximal embrasure.

The restorative material ACTIVA™ BioACTIVE (Pulpdent MA, USA) or Dyract® eXtra (DENTSPLY, Germany) was chosen according to the randomization and placed in the cavity according to the manufacturer's instructions.

For Dyract, the internal cavity surface was etched with 35% phosphoric acid (Ultra-Etch®) for 20 seconds and then washed and dried. A bonding agent (Prime & Bond NT - DENTSPLY) was applied and cured for 10 seconds. The material was placed in layers, 2mm each.

In case of ACTIVA, the surface was only etched with 35% phosphoric acid (Ultra-Etch®). No bonding agent was used and the material was placed in layers up to 4mm.

Both materials were cured using light cure source (Satelec Mini LED curing light - light intensity 1250 mW/cm^2, wave length 420 – 480 nm) for 20 seconds. The material was then finished and polished, and the cavity margins were checked for any voids, gaps or overhanging and the occlusion was checked for any high points.

A post-operative digital bitewing radiograph was taken immediately after the treatment as a base line reference and to check for voids or any defect in the restoration.

6.8 Time needed for placement

After preparing the cavity and placing the matrix band and wedge, the time was recorded until the end of finishing and polishing to investigate whether both materials take the same time to be placed in the oral cavity.

6.9 Follow up & evaluation

In the six months follow up visit, the teeth were evaluated clinically as well as radiographically by two calibrated and blinded evaluators (pedodontists J.V. and J.V.A.) other than the operator. Both evaluators were blinded and had no information about the type of material to be evaluated.

6.9.1 Evaluators' calibration

Before calibrating the two evaluators, both of them have received detailed explanation and training about the evaluation criteria used in this study. The explanation included clinical pictures representing each different score for each criterion. The exercise was done on 20 clinical pictures and 10 restored (class II) Frasaco teeth with different clinical situations. The calibration was performed by asking the evaluators separately to score 20 clinical pictures and 10 restored (class II) Frasaco teeth with various clinical situations (successful, accepted and failed restorations). The clinical photos and Frasaco teeth which used for exercise were not the same ones used for calibration.

The results of each evaluator were compared to a benchmark examiner with higher educational and experience level (L.M.) to assess the scoring accuracy. This was done because both evaluators may have a high inter-evaluator agreement but the scoring of both of them may be incorrect. Inter- evaluator agreement was assessed through comparing the results against each other. After 2 weeks, the evaluators were asked to score the same clinical pictures and Frasaco teeth in order to determine the intra- evaluator agreement.

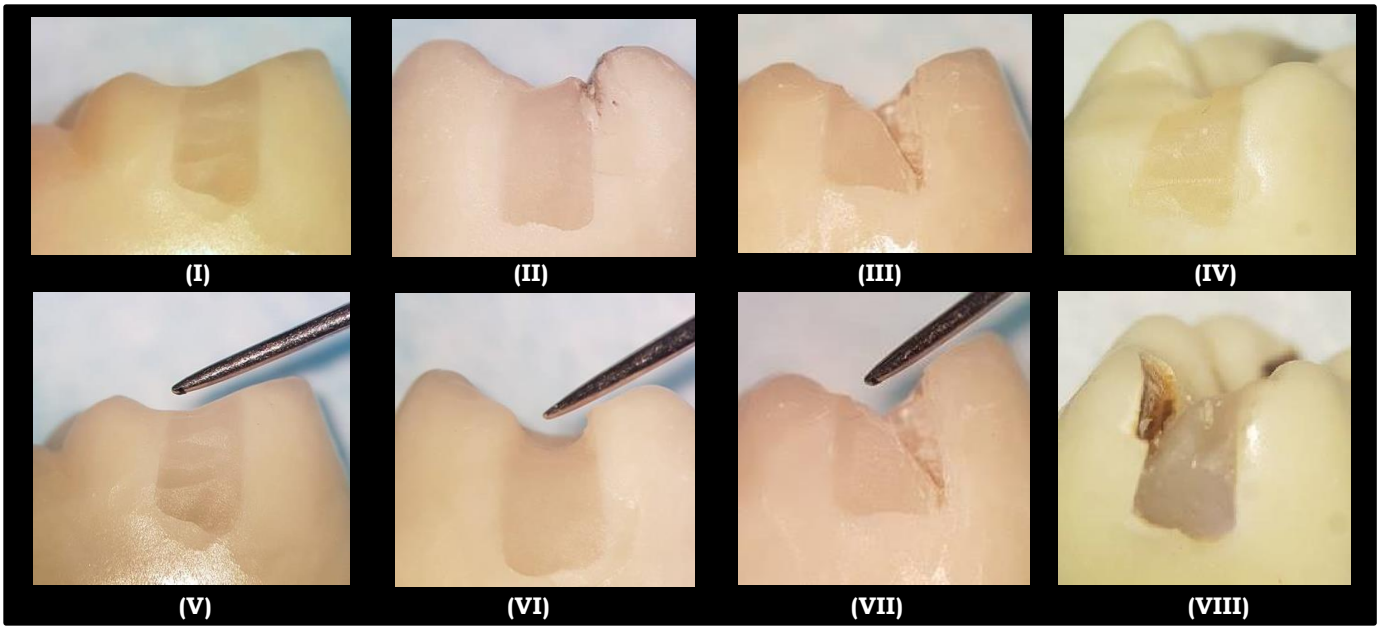


Figure 4: Some clinical situations demonstrated by Frasaco teeth. **(I)** Best clinical situation (score A). **(II)** Marginal integrity is not ideal, explorer falls into crevice but the dentine is not exposed (score B). **(III)** Marginal integrity is lost, dentine is exposed and the filling is partially lost (score C). **(IV)** Small tooth fracture (cusp), but the filling is retained (score B). **(V)** The contour of the restoration follows the contour of the tooth (using explorer) (score A). **(VI)** A surface concavity is present but the dentine is not exposed (score B). **(VII)** Loss of restoration and the dentine is exposed (score C). **(VIII)** Both filling and tooth are fractured with secondary caries (score C).

6.9.2 Evaluation criteria

All included teeth were evaluated by two blinded and calibrated evaluators using modified United States Public health Service (USPHS) Ryge Criteria for direct clinical evaluation of tooth colored restorations (Table 4) (69). The included criteria were: color match, Marginal discoloration, Marginal adaptation, Anatomic form, Gross fracture (restoration), Fracture of tooth, Postoperative sensitivity, Secondary caries and Endodontic complications.

Each criterion had three scores: Alpha (A) = Ideal clinical restoration, Bravo (B) = acceptable clinical situation, and Charlie (C) = clinically unacceptable restorations (failure). The last two criteria have only 2 scores: Alpha (A) = Ideal clinical restoration and (C) = clinically unacceptable restorations (failure).

In order to determine the success and failure rate, the categorical outcome variables were reformed to become dichotomous variables. Both Alpha (A) and Bravo (B) scores were considered as clinical success and the score Charlie (C) was recorded as failure.

All restored teeth were also evaluated radiographically based on a six months radiograph which was compared to the base line radiograph to determine any defect in the material

which could be due to improper placement of restoration. The radiographic criterion was: Secondary caries. Those criteria were scored as either present or not present. Both evaluators had no information about the type of material in the radiograph.

Table 4: Modified USPHS Ryge Criteria for clinical evaluation of tooth colored restoration (69)

Characteristic	Criteria		
	Alpha (A)	Bravo (B)	Charlie (C)
Color match	No mismatch in color, shade and translucency between the restoration and the adjacent tooth structure.	Mismatch within the normal range.	Mismatch outside the normal range.
Marginal discoloration	No marginal discoloration between the restoration and the adjacent tooth structure.	There is marginal discoloration but doesn't penetrate pulpally.	Marginal discoloration penetrates pulpally.
Marginal adaptation (integrity)	Explorer doesn't catch when drawn across the restoration/tooth interface.	Explorer falls into crevice, dentine is not exposed.	Dentine or base is exposed.
Anatomic form	The contour of the restoration follows the contour of the tooth or slightly flattened.	Surface concavity but the dentine is not exposed.	Loss of restoration and the dentine is exposed.
Gross fracture	Restoration is intact and fully retained.	Restoration is partially fractured but still retained.	Restoration is missing.
Tooth fracture	No tooth fracture	Small tooth fracture but the filling is retained.	Gross tooth fracture with exposure of dentine.
Post-operative sensitivity	Not present.	Sensitive but diminishing in intensity.	Constant sensitivity.
Secondary caries	No secondary caries.	There is secondary caries.	
Endodontic complications abscess, fistula, swelling etc.	Not present.	Present.	

6.10 Other conditions

Other conditions like normal exfoliation, caries in another tooth surface, and severe gingival inflammation are not considered as failure because they are not related or caused by the restoration.

6.11 Statistical analysis

Inter- and intra- evaluator agreement was calculated using Cohen's Kappa statistical test and the values were interpreted using Landis & Koch scores 1977 (Table 5) (70). Data analysis was performed using Statistical Package for Social Sciences (IBM corp. SPSS Statistics for Windows, Version 25.0. Armonk, NY). Significance level was set at ($P < 0.05$).

Since the design was split mouth, some variables were equal between the treatment groups (i.e. age, gender, PI, DMFT and dmft). Therefore, only descriptive statistics were performed to report those variables.

The McNemar's test was used to compare between the binary outcome variables (success/failure) based on the modified USPH Ryge criteria.

Paired-samples *t*-test was performed to analyze the continuous outcome variable (time needed to place each material) against the type of material (ACTIVA or Dyract), jaw (Upper or lower) and molar treated (first or second molar). The normality of the residuals was checked visually by histogram, and all residuals were normally distributed.

Table 5: Scores interpretation according to Landis & Koch

Score	0	0 - 0.2	0.21 - 0.4	0.41 - 0.6	0.61 - 0.8	0.81 - 1
Value	Poor	Slight	Fair	Moderate	Substantial	Almost prefect

7. Results

7.1 Baseline assessment

After applying the inclusion and exclusion criteria, a total number of 80 class II restorations (40 per group, ACTIVA and Dyract) were placed by one operator in primary molars of twenty children aged between 5 and 10 years with a mean (± SD) age of 7.3 (± 1.49) years, based on split mouth design (table 6).

The baseline assessment of oral hygiene status showed a mean PI of 1.48 (± 1.6), which considered fair. The baseline values of DMFT and dmft were 0.35 (± 0.74) and 6.55 (± 2.25) respectively (Table 7).

Table 6: Baseline descriptive characteristics

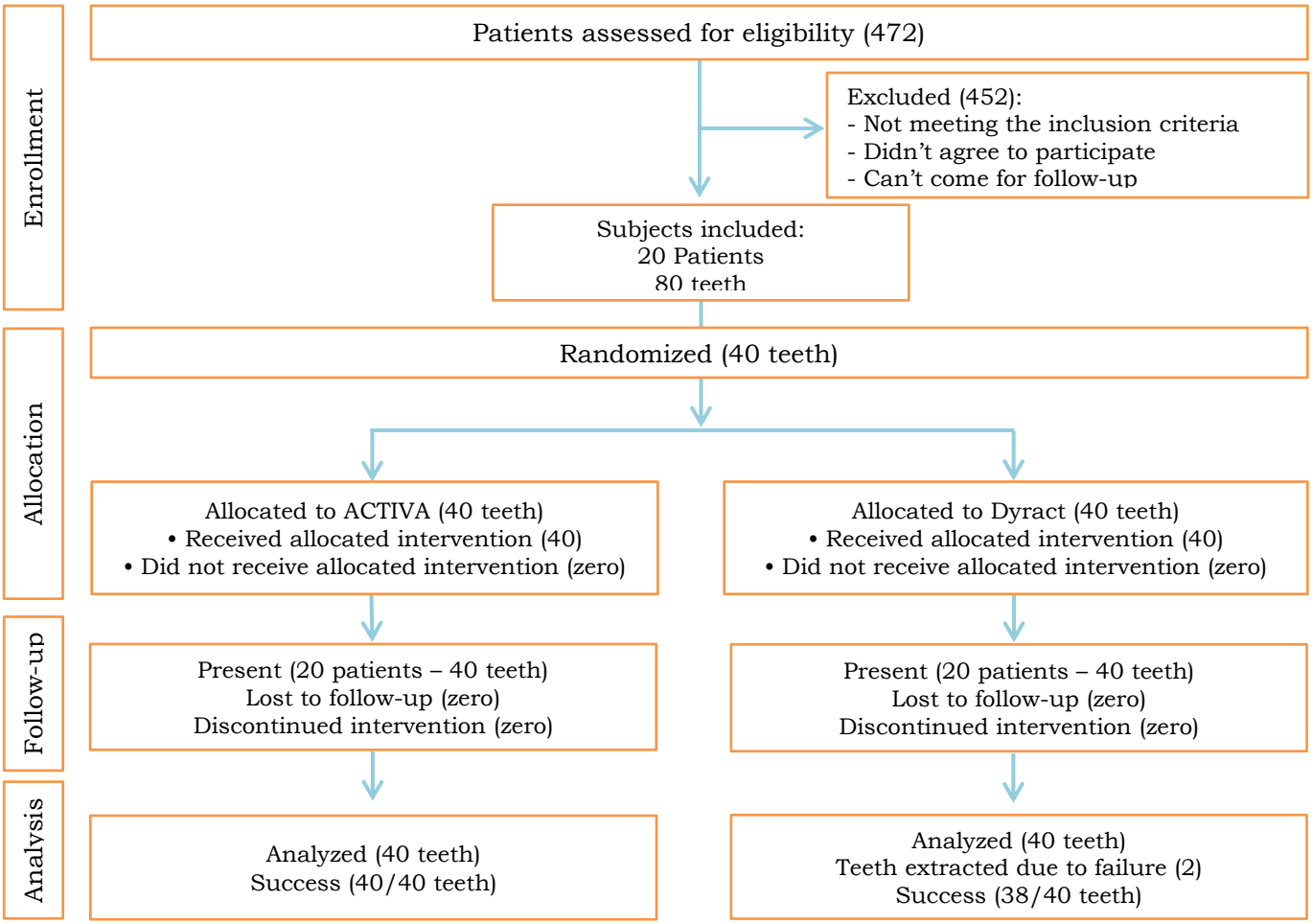
	Value								Total
Age	mean 7.3				SD 1.49				-
Per gender	male 5				female 15				20
Per Subjects treated	children 20				Teeth 80				-
Per material	ACTIVA 20				Dyract 20				80
Per jaw	maxillary 44				Mandibular 36				80
Per molar	First molar 44				Second molar 36				80
Per tooth	55 11	54 11	64 11	65 11	75 4	74 9	84 13	85 10	80

Table 7: Baseline oral hygiene status

	Mean	SD
PI	1.48	1.6
DMFT	0.35	0.74
dmft	6.55	2.25

7.2 Participants and inter-evaluator agreement

The flow of the participants through enrollment, allocation, follow-up and analysis is showed in (Flow chart 2). At the six months follow-up all children were present for evaluation and the drop-out rate was 0%. The result of Cohen's kappa (κ) for inter- and intra- evaluator agreement was 0.75 (substantial) and 0.81 (almost perfect) respectively (according to Landis & Koch interpretation) (Table 8).



Flow chart 2: Flow of participants according to CONSORT

Table 8: Cohen's kappa (κ) and Landis & Koch scores for inter- and intra- rater agreement

	Inter-rater	Intra-rater	
		J.V	J.V.A
Cohen's kappa (κ)	0.75	0.81	0.81
Landis & Koch scores	substantial	almost perfect	almost perfect

7.3 Outcome results

Two teeth restored with Dyract were extracted due to pain and abscess. The rest of the evaluated teeth in both groups were clinically and radiographically successful. The overall success of ACTIVA and Dyract was 100% and 95% respectively. There was no statistical significant difference between the success rate of both materials at 6 months follow-up (McNemar's test) (Table 9).

There was a statistically significant difference regarding the time needed to place the material. Activa took a mean of 2.37 (± 0.63) minutes less than Dyract to be laced in the oral cavity (*t*-test $P < 0.001$). There was no statistically significant difference between neither the upper and lower jaw nor between the first and second molar regardless the type of material (Table 10).

Table 9: Clinical and radiographic success at 6 months follow-up

	Clinical success									Radiographic success	Overall success
	Color match	Marginal discoloration	Marginal adaptation	Anatomic form	Gross fracture	Tooth fracture	Post-operative sensitivity	Secondary caries	Endodontic complications	Secondary caries	
ACTIVA N (%)	40	40	40	40	40	40	40	40	40	40	40 (100)
Dyract N (%)	40	40	40	40	40	40	38	40	38	40	38 (95)
											$P > 0.05$*

N = number of teeth which were successful
*McNemar's test

Table 10: Time needed to place the filling material

	Mean minutes (SD)		Mean difference (SD)	sig
Per material	ACTIVA 4.19 (0.4)	Dyract 6.65 (0.39)	2.37 (0.63)	$P <$ 0.001*
Per jaw Regardless the type of material	Maxillary 5.42 (1.33)	Mandibular 5.39 (1.22)	0.03 (2.03)	$P > 0.05$
Per molar Regardless the type of material	First molar 5.42 (1.22)	Second molar 5.33 (1.31)	0.08 (2.48)	$P > 0.05$

Paired-samples t-test
* Statistically significant

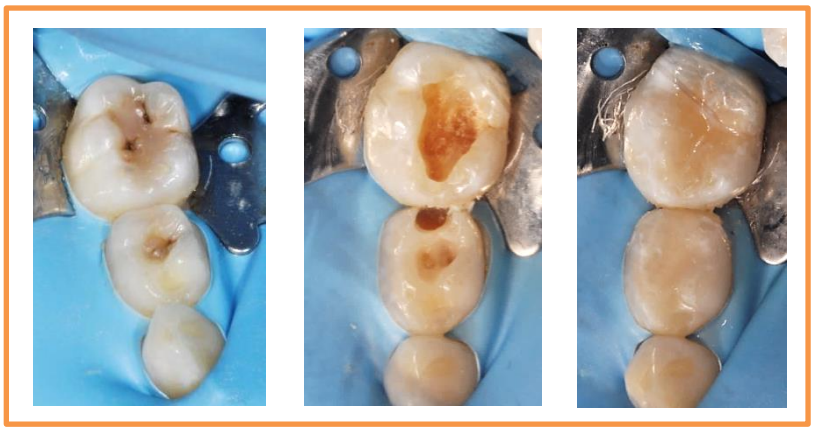


Figure 5: Clinical demonstration of caries, cavity preparation and final restoration.
Only the first primary molar was included in this patient (Class II cavity)

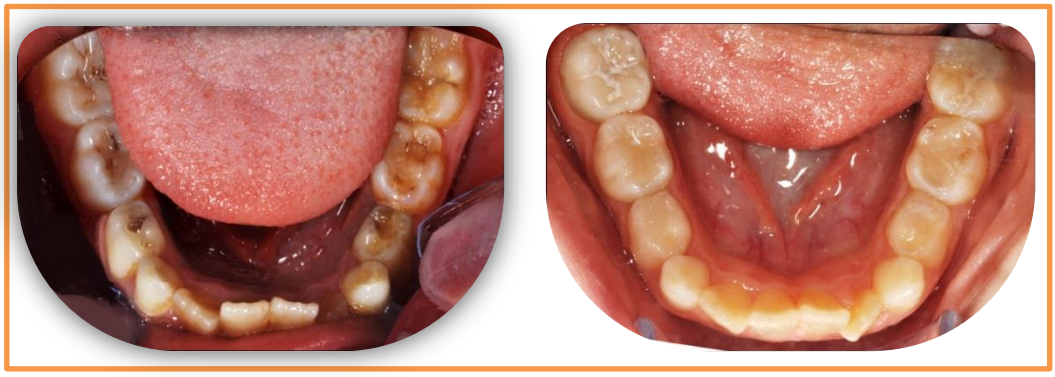


Figure 6: Clinical demonstration of split mouth design.
Only the first primary molars were included in this patient (Class II cavities)

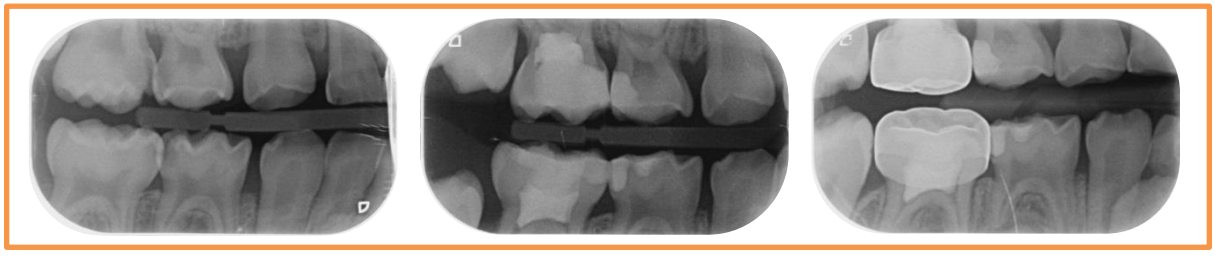


Figure 7: Pre-, post-operative and follow-up X-rays.
Only the first primary molars were included in this patient

8. Discussion

8.1 Study design

A split-mouth randomized controlled trial (RCT) design was used in this study. In comparison to parallel arms RCT design, split-mouth RCTs have the advantage that most of the variability of outcomes among patient level (e.g. age, gender, socio-economic status and other demographic parameters) is neglected from the intervention effect for a potential increase in the statistical power. Furthermore, each subject acts as its own control, and the required sample size is usually smaller than parallel arms RCTs (71).

The split-mouth RCTs may have on the other hand some limitations such as carry-across effect or contamination of one intervention in one side by the other intervention from the other side of the mouth (72). In this study, this was not the case as the effect of each intervention is confined to the restored tooth.

Period effects could be also a shortcoming for this type of design when interventions are not delivered simultaneously and the effect of the intervention is influenced by the period of delivery, as some conditions (e.g. pain, gingival or periodontal inflammation) may improve with time before implementing the second intervention, leading eventually to false positive – or success- results (72). However, the condition (caries) in this study couldn't be improved or changed with time whatsoever, and won't get worse drastically as the time period of delivering both interventions was within 3 weeks and each tooth was re-evaluated at each step for inclusion and exclusion criteria until placement of the filling material.

Another problem may be encountered for split-mouth RCTs when it is difficult to find and recruit appropriate patients having the same condition on both sides of the mouth with similarity between randomization units, especially for studies where the pulp or root canal system is included in the methodology and the units have to be similar on both sides because of variation in root morphology between different teeth (72). In attempt to overcome this difficulty, the recruitment period was prolonged in order to reach the required sample size. Moreover, the pulp system is not involved in the intervention. Therefore, this drawback was relatively not a big issue.

8.2 Patient recruitment

The calculated sample size was 35 teeth per group. This was based on the success rate of Dyract from studies in the literature with similar methodology. The success rate of ACTIVA was based on the pilot study. The sample size was at the tooth level and not on the patient level.

The reported sample size regarding the success of Dyract varied in several studies and ranged between 14 and 104 teeth per group with a mean of 50 teeth per group (10-23). Because split-mouth design requires less number of units, 40 teeth per group were assumed to be enough in this trial after adjustment for a possible dropout rate.

Eventually forty restorations per group were placed in twenty children. All children were present in the six months follow-up appointment with no dropout. This is probably because all of them were regular patients in the University Hospital and they were not referred from another clinic. The follow-up period was also not too long where the dropout is an expected event.

8.3 baseline assessment and intervention

The baseline oral hygiene status for PI was 1.48 (± 1.6), and for DMFT and dmft was 0.35 (± 0.74) and 6.55 (± 2.25) respectively, indicating high caries experience with fair oral hygiene. This could be due to the inclusion criteria, as most of the patients with lower dmft scores wouldn't have caries on both sides of the mouth and therefore they will not be included in the study. Moreover, when caries is present on both sides, mostly its interdental and both first and second primary molars are affected which would end up eventually with higher dmft scores. Therefore, the clinical applicability of the results in the general population should be cautiously interpreted.

All restorations were class II in primary molars and were placed by one operator to exclude inter-operator bias. The operator was a master student who was trained to place both materials in primary dentition. All children were treated in the dental chair under the same clinical settings with rubberdam isolation; thereby avoid any confounding factor that may affect the treatment outcome.

8.4 Follow-up and evaluation

Both evaluators were trained and calibrated to evaluate the teeth based on modified USPH Ryge criteria (most widely used) using clinical pictures, models and Frasaco teeth. The criteria were sophisticated and the borders between the scores were sometimes vague. Nevertheless, the inter- and intra-evaluator agreement was 0.75 (substantial) and 0.81 (almost perfect) respectively. The scores of both evaluators were also compared against a bench mark rater with higher educational and experience level (L.M.) to check the accuracy, which were also substantial.

Regarding USPH criteria, both scores "A and B" were combined and considered as "success". Score "C" was considered as "failure". The purpose behind this adjustment was to interpret the results more easily as "success and failure", and due to the lack of difference between score "A" and "B" in both groups, at least for the six months follow-up period. This adjustment was also performed in both studies done by Ertugrul F et al. (2010) (21) and Ghaderi F and Mardani A (2015) (22).

Out of 40 teeth, two primary first molars restored with Dyract had endodontic complications (pain, abscess and inter-radicular radiolucency) and had to be extracted, resulting in a success rate of 95%, which was not significantly different from ACTIVA. There was no secondary caries or fracture and the filling was in place. The reason behind this failure could be that the pulp was already infected by bacterial infiltration which couldn't be detected visually, also preparing and etching the tooth may cause irritation to the pulp system, which ended up with pulpitis, although the tooth was asymptomatic, the caries wasn't extended to the pulp, there was no inter-radicular radiolucency and no pulp exposure after tooth preparation.

These results regarding the success of Dyract were consistent with other studies, Hse KM and Wei SH (1997) reported 95% for 12 months period (11), Gross LC et al. (2001) reported 96% for 24 months (17) and 95.7% for 24 months by Ertugrul F et al. (2010) (21).

Other studies have reported different success rate which ranged between 78% and 96% (mean 87%) (10-23). One meta-analysis investigated the success rate of class II Compomer restorations in primary molars and reported 87% for 1 to 3 years follow-up (20). A systematic review reported a success rate of 91%. However, this percentage was for both class I and II

restorations, where class I restorations had better success rate, indicating a success rate lower than 91% for class II restorations (23).

The variation of this value is probably due to several factors such as the follow-up period (one to three years), type of the study (split-mouth, RCT or non-RCT) where different statistical analysis is used, type of Compomer (Compoglass, Dyract or F 2000), operator experience and evaluator's reliability (73).

The patient may also play a role in this variation depending on the age and/or cooperation, as very young children could be difficult to treat in the chair which may affect the quality of the treatment in comparison to older or cooperative children. One article reported a survival rate of 51% of class II restorations over 5 years follow-up under the age of four years, and the survival rate was 70% in children over this age. Moreover, a median survival time of restorations placed in 3 years old children was 11 months. This value was increased to 44 months in children aged 7 to 8 years (74). In this study, only cooperative children aged between 5 to 10 years were included.

The caries risk has also an effect on the treatment outcome especially in patients with active caries or high caries experience in both primary and permanent dentition. In a study in 2010, RBC showed better survival rate than amalgam in the permanent dentition in 12 years follow-up in patients with low caries risk, while amalgam showed better performance in high caries risk, especially after 5-8 years. Caries as a reason for failure was more frequent with RBC than with amalgam, especially in the high-risk group (75). According to Chisini LA et al. (2018), the main reason for failure observed for Compomer in the primary dentition was secondary caries (23). In the current study, secondary caries was not observed, possibly due to the short follow-up period.

Furthermore, the lack of using rubberdam and the larger number of involved surfaces have a negative influence on the success of restorative materials. A systematic review showed that Class I restorations and restorations placed using rubber dam have better annual failure rate (23). One study reported that every extra surface involved in a restoration increases the risk for failure by 30-40% (76).

Variability of sample size could be another factor implicated in the variability of success percentage among studies. In case of small sample size, one tooth failure gives rise to magnified failure percentage. Whereas in larger sample size, bigger number of failed teeth is required in order to produce the same failure percentage as the small group size. Hence, it is recommended to report the success rate together with the number of teeth for more accurate interpretation.

There are no published data in the literature about the *in vivo* success rate of ACTIVA. The present study is the first one to evaluate ACTIVA in a clinical trial and report 100% success. The high success rate could be attributed to the short follow-up period, strict clinical procedure or the validity of the material to perform in the oral cavity as a permanent filling. This emphasizes the need for more long-term clinical studies.

The included patient group was at high caries risk, which doesn't represent the general population and may generate skewed results. Thus, more studies considering different grades of caries experience is beneficial to draw more accurate results. Nevertheless, if a restorative material would survive in a high caries risk group, then it will certainly perform equal or better in lower risk groups where the bioactivity is important to prevent secondary caries.

8.5 Time needed for placement

ACTIVA took significantly 2.37 (± 0.63) minutes less than Dyract to be placed in the oral cavity. The difference in time is owing to the step of applying and curing bonding agent before placing Dyract, which is not compulsory for ACTIVA. Besides, Dyract had to be placed in layers 2mm each, while ACTIVA could be placed up to 4mm. This could be due to the monomer composition or the chemical cure resin in ACTIVA which allows the material to set fully even in the deeper layer (40). Whereas, light cure is essential for Dyract to initiate the setting reaction (6). In addition to that, Dyract has to be condensed in the cavity and adjustment with plastic and/or other instrument was important to mold the anatomy, in contrast to ACTIVA which is flowable, less handling was required to restore the cavity, resulting in shorter working time. Taking into account that the cavity in the current study is only class II, meaning that no cusp build up or large restoration was involved which may give different results for flowable materials.

The time difference of 2.37 minutes between the two materials on one hand might be of less clinical significance if we compare it to the whole dental visit (30 to 45 minutes). On the other hand, those two minutes are tangled in the most critical part of the dental visit where the procedure is sensitive, the cavity should be dry, the child usually has been on the chair for a while, should stay still, keep his mouth open and most often becomes tired. Therefore, a two minutes period could be interesting to shorten this sensitive period.

ACTIVA possesses the ability to bond to tooth structure through the ionization of the phosphate group in the filling material and forming an ionic bond with the tooth structure. Therefore, the use of bonding agent is not as crucial as it is with Dyract (40). Garcia-Godoy F and Morrow B (2016) showed that ACTIVA has produced resin tags integrating into dentinal tubules, which is responsible for enhanced seal (52). Additionally, applying a layer of bonding may hinder the bioactivity and the integration between the filling and tooth structure. Although, Murali S et al. (2016) reported that the released F ions from ACTIVA can penetrate through the bonding agent. However, the bioactivity of the material covered with bonding was never tested (58).

There was no difference in the duration of placing the filling material between upper and lower jaw, or between the first and second primary molar, regardless the type of the material, which could be as a result of equal distribution and randomization of materials in both sides among the whole dentition.

It should be noted that the time was calculated after finishing the tooth preparation and placing the matrix band. The preparation time was therefore not included. Hence, variation in the duration of the whole restoration procedure between different teeth may be present.

8.6 Study limitations

The operator was not blinded for the randomization during material placement, as both interventions have different application procedure. Yet, the randomization was concealed during tooth preparation and was declared after placing the matrix band.

The follow-up period was too short to establish conclusive results regarding the success of both materials. However, this project provides more information and better sight for future longer follow-up trials.

The efficiency of the bioactive properties of ACTIVA couldn't be demonstrated in the final results, probably due to the short follow-up period. Therefore, longer follow-up clinical studies accompanied by *in vitro* studies are important to know how far a bioactive restorative material could be helpful in preventing secondary caries and to understand better the relation between bioactivity and prevention of secondary caries.

9. Conclusion

Within the limitations of this study, it can be concluded that both groups (ACTIVA and Dyract) had an excellent performance as a permanent restorative material in vital primary molars with class II cavity in children with high caries risk in a period of 6 months, and the null hypothesis (H_0) could be accepted. More randomized controlled trials with adequate sample size and longer follow-up period is essential to validate the long term success of the therapy.

ACTIVA took significantly less time than Dyract to be placed in the oral cavity, which could be of an interest for the dentist to reduce the chairside time while the child has to keep his mouth open.

10. References

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11.1 Ethical committee approval

Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

Afz: Commissie voor Medische Ethiek (UZP074)

COMMISSIE VOOR MEDISCHE ETHIEK

Tand-, mond- en kaakziekten
Poliklinickgebouw 8 - gelijkvloers
Prof. dr. Luc MARTENS
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Voorzitter:
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UW KENMERK	**ONS KENMERK**	**DATUM**	**KOPIE**
	2016/1050	23-dec-16	Zie "CC"

BETREFT Advies voor monocentrische studie met als titel:
COMPARISON OF ACTIVA™ BIOACTIVE VERSUS COMPOMER FOR CLASS II RESTORATION IN PRIMARY MOLARS: A 24 MONTHS RANDOMIZED CLINICAL TRIAL.
Belgisch Registratienummer: B670201629533
Fase (Phase): NVT/NA

* Adviesaanvraagformulier dd. 2/09/2016 (volledig ontvangen dd. 14/09/2016) + aangepaste versie ontvangen dd. 16/11/2016
  Begeleidende brief dd. 29/08/2016
  Protocol
  Bijsluiter
    product informatie
    componer product informatie
* Antwoord onderzoekers: mail ontvangen 16/11/2016 in antwoord op opmerkingen EC dd. 13/10/2016 en defintief antwoord ontvangen op 22/12/2016 (laatste aanpassingen aan het ICF)
* Patiënteninformatie- en toestemmingsformulier: definitieve versie ontvangen 22/12/2016 versie 22/12/2016.

Advies werd gevraagd door: Prof. dr. L. MARTENS ; Hoofdonderzoeker

BOVENVERMELDE DOCUMENTEN WERDEN DOOR HET ETHISCH COMITÉ BEOORDEELD.
ER WERD EEN POSITIEF ADVIES GEGEVEN OVER DIT PROTOCOL OP 22/12/2016. INDIEN DE STUDIE NIET WORDT OPGESTART VOOR 22/12/2017, VERVALT HET ADVIES EN MOET HET PROJECT TERUG INGEDIEND WORDEN.
Vooraleer het onderzoek te starten dient contact te worden genomen met Bimetra Clinics (09/332 05 00).

THE ABOVE MENTIONED DOCUMENTS HAVE BEEN REVIEWED BY THE ETHICS COMMITTEE.
A POSITIVE ADVICE WAS GIVEN FOR THIS PROTOCOL ON 22/12/2016. IN CASE THIS STUDY IS NOT STARTED BY 22/12/2017, THIS ADVICE WILL BE NO LONGER VALID AND THE PROJECT MUST BE RESUBMITTED.
Before initiating the study, please contact Bimetra Clinics (09/332 05 00).

DIT ADVIES WORDT OPGENOMEN IN HET VERSLAG VAN DE VERGADERING VAN HET ETHISCH COMITE VAN 17/01/2017
THIS ADVICE WILL APPEAR IN THE PROCEEDINGS OF THE MEETING OF THE ETHICS COMMITTEE OF 17/01/2017

- *Het Ethisch Comité werkt volgens 'ICH Good Clinical Practice' - regels*
- *Het Ethisch Comité beklemtoont dat een gunstig advies niet betekent dat het Comité de verantwoordelijkheid voor het onderzoek op zich neemt. Bovendien dient U er over te waken dat Uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.*
- *In het kader van 'Good Clinical Practice' moet de mogelijkheid bestaan dat het farmaceutisch bedrijf en de autoriteiten inzage krijgen van de originele data. In dit verband dienen de onderzoekers erover te waken dat dit gebeurt zonder schending van de privacy van de proefpersonen.*
- *Het Ethisch Comité benadrukt dat het de promotor is die garant dient te staan voor de conformiteit van de anderstalige informatie- en toestemmingsformulieren met de Nederlandstalige documenten.*
- *Geen enkele onderzoeker betrokken bij deze studie is lid van het Ethisch Comité.*
- *Alle leden van het Ethisch Comité hebben dit project beoordeeld. (De ledenlijst is bijgevoegd)*

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	2016/1050	23-dec-16	Zie "CC"

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° *The Ethics Committee stresses that it is the responsibility of the promotor to guarantee the conformity of the non-Dutch informed consent forms with the Dutch documents.*

° *None of the investigators involved in this study is a member of the Ethics Committee.*

° *All members of the Ethics Committee have reviewed this project. (The list of the members is enclosed)*

Namens het Ethisch Comité / On behalf of the Ethics Committee

Prof. dr. D. MATTHYS
Voorzitter / Chairman

CC: De heer T. VERSCHOORE - UZ Gent - Bimetra Clinics
FAGG - Research & Development; Victor Hortaplein 40, postbus 40 1060 Brussel

Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

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COMPARISON OF ACTIVA™ BIOACTIVE VERSUS COMPOMER FOR CLASS II RESTORATION IN PRIMARY MOLARS: A 24 MONTHS RANDOMIZED CLINICAL TRIAL. (scriptie Reda Banon)
Belgisch Registratienummer: B670201629534
Fase (Phase): NVT/NA

* Adviesaanvraagformulier dd. 2/09/2016 (volledig ontvangen dd. 14/09/2016) + aangepaste versie ontvangen dd. 16/11/2016
* Adviesaanvraagformulier (type E) dd. 8/09/2016 (volledig ontvangen dd. 14/09/2016
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UW KENMERK	**ONS KENMERK**	**DATUM**	**KOPIE**
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Vervolg blz. 2 van het adviesformulier betreffende project EC UZG 2016/1051

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Voorzitter / Chairman

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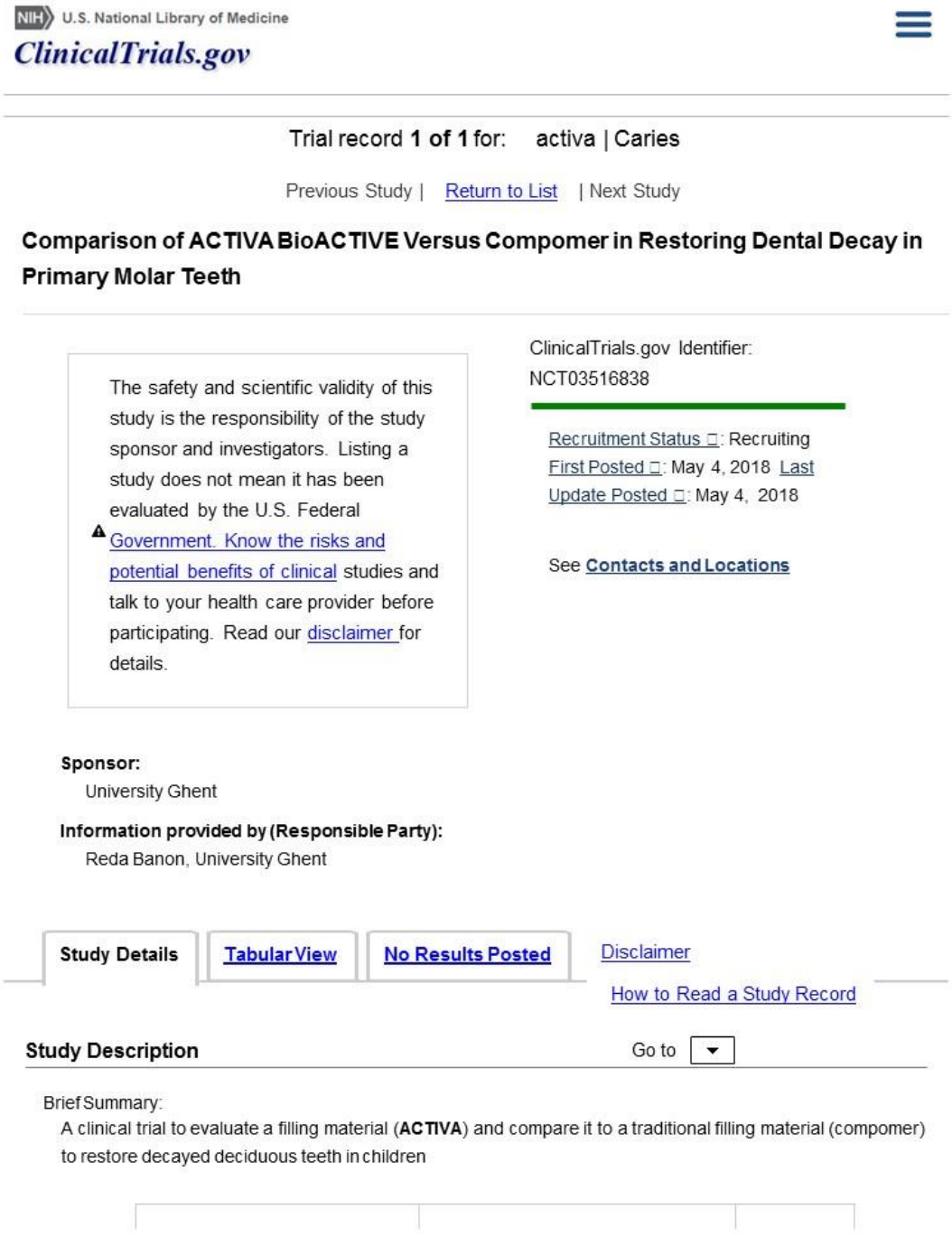
FAGG - Research & Development; Victor Hortaplein 40, postbus 40 1060 Brussel

11.2 Trial registration



NIH U.S. National Library of Medicine
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Trial record 1 of 1 for: activa | Caries

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Comparison of ACTIVA BioACTIVE Versus Compomer in Restoring Dental Decay in Primary Molar Teeth

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03516838

Recruitment Status : Recruiting
First Posted : May 4, 2018 Last Update Posted : May 4, 2018

See **Contacts and Locations**

Sponsor:
University Ghent

Information provided by (Responsible Party):
Reda Banon, University Ghent

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to

Brief Summary:
A clinical trial to evaluate a filling material (**ACTIVA**) and compare it to a traditional filling material (compomer) to restore decayed deciduous teeth in children

11.3 Informed consent

Toestemmingsformulier

Ik, _____ heb het document "Informatiebrief voor de ouders of de voogd" pagina 1 tot en met pagina 2 gelezen en er een kopij van gekregen. Ik stem in met de inhoud van het document en stem ook in om mijn kind te laten deelnemen aan de studie.

Ik heb een kopij gekregen van dit ondertekende en gedateerde formulier voor "Toestemmingsformulier". Ik heb uitleg gekregen over de aard, het doel, de duur, en de te voorziene effecten van de studie en over wat men van mij en mijn kind verwacht. Ik heb uitleg gekregen over de mogelijke risico's en voordelen van de studie. Men heeft me de gelegenheid en voldoende tijd gegeven om vragen te stellen over de studie, en ik heb op al mijn vragen een bevredigend antwoord gekregen.

Ik stem ermee in om volledig samen te werken met de toeziende arts Prof. Dr. Rita Cauwels. Ik zal haar op de hoogte brengen als mijn kind onverwachte of ongebruikelijke symptomen ervaar.

Men heeft mij ingelicht over het bestaan van een verzekeringspolis in geval er letsel zou ontstaan dat aan de studieprocedures is toe te schrijven.

Ik ben me ervan bewust dat deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan het UZ Gent en dat deze studie zal uitgevoerd worden volgens de richtlijnen voor de goede klinische praktijk (ICH/GCP) en de verklaring van Helsinki, opgesteld ter bescherming van mensen deelnemend aan experimenten. Deze goedkeuring was in geen geval de aanzet om te beslissen om mijn kind te laten deelnemen aan deze studie.

Ik mag mijn kind op elk ogenblik uit de studie terugtrekken zonder een reden voor deze beslissing op te geven en zonder dat dit op enigerlei wijze een invloed zal hebben op mijn verdere relatie met de arts Prof. Dr. Rita Cauwels**.**

Men heeft mij ingelicht dat zowel persoonlijke gegevens als gegevens aangaande de gezondheid van mijn kind, worden verwerkt en bewaard gedurende minstens 20 jaar. Ik stem hiermee in en ben op de hoogte dat ik recht heb op toegang en verbetering van deze gegevens. Aangezien deze gegevens verwerkt worden in het kader van medisch-wetenschappelijke doeleinden, begrijp ik dat de toegang tot de gegevens van mijn kind kan uitgesteld worden tot na beëindiging van het onderzoek. Indien ik toegang wil tot de gegevens van mijn kind, zal ik mij richten tot de toeziende arts Prof. Dr. Rita Cauwels, die verantwoordelijk is voor de verwerking.

Ik begrijp dat auditors, vertegenwoordigers van de opdrachtgever, de Commissie voor Medische Ethiek of bevoegde overheden, de gegevens van mijn kind mogelijk willen inspecteren om de verzamelde informatie te controleren. Door dit document te ondertekenen, geef ik toestemming voor deze controle. Bovendien ben ik op de hoogte dat bepaalde gegevens doorgegeven worden aan de opdrachtgever. Ik geef hiervoor mijn toestemming, zelfs indien dit betekent dat de

gegevens van mijn kind doorgegeven worden aan een land buiten de Europese Unie. Ten alle tijden zal de privacy van mijn kind gerespecteerd worden.

Ik ben bereid mijn kind op vrijwillige basis te laten deelnemen aan deze studie.

Naam van het kind ……..

Naam ouder/voogd ……..

Telefoon nummer .....

E-mail adres .....

Datum: _____

Handtekening:

Ik bevestig dat ik de aard, het doel, en de te voorziene effecten van de studie heb uitgelegd aan de bovenvermelde vrijwilliger.

De vrijwilliger stemde toe zijn/haar kind te laten deelnemen door zijn/haar persoonlijk gedateerde handtekening te plaatsen.

Naam van de persoon
die voorafgaande uitleg
heeft gegeven: _____

Datum: _____

Handtekening:

INFORMATIEBRIEF VOOR DE OUDERS OF DE VOOGD

In het kader van het onderzoek getiteld *"Vergelijking van het bioactieve materiaal ACTIVA ™ versus een compomeer voor klasse II restauratie in melkmolaren: Een gerandomiseerde klinische trial"*

Geachte ouders / voogden,

Wij vragen u vriendelijk om mee te doen aan ons wetenschappelijk onderzoek. U beslist zelf of uw kind mee mag doen. Voordat u een beslissing neemt, is het belangrijk om meer te weten over het onderzoek. Leest u rustig deze informatiebrief.

Wat is het doel van het onderzoek ?

Cariës (gaatjes) in het melkgebit moeten eveneens behandeld worden. Tegenwoordig zijn er verschillende nieuwe materialen beschikbaar met bio actieve eigenschappen. Deze eigenschappen kunnen nieuwe cariës vermijden. In dit onderzoek willen wij het succes van een bio actief vullingmateriaal (ACTIVA™ BioACTIVE Restorative –PULPDENT) vergelijken met ons traditioneel vullingsmateriaal (compomeer Dyract eXtra - DENTSPLY).

Achtergrond van de verschillende producten

Een compomeer is een materiaal dat reeds uitgebreid onderzocht werd en zijn succes bewezen heeft in het melkgebit.
ACTIVA™ BioACTIVE is een nieuw materiaal met specifieke eigenschappen. Het materiaal heeft een constante vrijstelling en opname van fluoride waardoor nieuwe cariësontwikkeling kan vermeden worden. Tot op heden bestaan er geen klinische studies in het melkgebit met dit materiaal. Het werd wel reeds onderzocht in het volwassen gebit.

Hoe wordt het onderzoek uitgevoerd ?

Wanneer tijdens de behandeling van uw kind een vulling nodig is zal een keuze gemaakt worden uit één van de twee producten: ACTIVA™ BioACTIVE of het klassieke compomeer. Tijdens de normale zesmaandelijkse controle wordt deze vulling extra beoordeeld naar kleur, randaanpassing, slijtage en vorm.

Hoe wordt die keuze tussen twee producten gemaakt ?

De keuze tussen één van de twee producten wordt bepaald door een computerlijst. Op die manier is er geen beïnvloeding mogelijk van het onderzoek.

Wat gebeurt er als u niet wenst deel te nemen aan dit onderzoek ?

Deelnemen is geheel vrijwillig en u en uw kind kunnen altijd aangeven te willen stoppen met het onderzoek. Een beslissing om de medewerking te beëindigen zal geen nadelige gevolgen hebben op verdere behandeling en geen invloed hebben op de zorg en aandacht waarop uw kind in onze polikliniek recht heeft.

Wordt u geïnformeerd als er afgeweken wordt van het studiemodel ?

De behandeling wordt volgens een wel bepaalde planning uitgevoerd. Als er een verandering plaats vindt en het heeft voor u directe gevolgen, dan brengen wij u hiervan op de hoogte. U beslist dan zelf of u met het onderzoek wilt stoppen of doorgaan.

Wat wordt er van u verwacht ?
Als u akkoord gaat om aan deze studie deel te nemen, vragen wij u, om tijdens de gewone 6 maandelijkse controle wat extra tijd te voorzien (10min).

Wat zijn de mogelijke nadelen van deelname aan dit onderzoek ?
U moet tijdens de controle extra tijd voorzien. Extra controle's zijn niet nodig.

Letsels tengevolge van deelname aan de studie:
De onderzoeker voorziet in een vergoeding en/of medische behandeling in het geval van schade en/of letsel tengevolge van deelname aan de studie. Hiertoe werd een verzekering afgesloten met foutloze aansprakelijkheid conform de wet inzake experimenten op de menselijke persoon van 7 mei 2004. Op dat ogenblik kunnen uw gegevens doorgegeven worden aan de verzekeraar.

Wat gebeurt er met uw gegevens ?
De verzamelde informatie van uw kind zal zeker vertrouwelijk behandeld worden. Tijdens en na de studie zullen wij uw identiteit en onderzoeksgegevens onder goed beveiligde omstandigheden beschermen.
In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal uw persoonlijke levenssfeer gerespecteerd worden en zal u toegang krijgen tot de verzamelde gegevens. Elk onjuist gegeven kan op uw verzoek verbeterd worden.
Vertegenwoordigers van de opdrachtgever, auditoren, de Commissie voor Medische Ethiek en de bevoegde overheden hebben rechtstreeks toegang tot uw medische dossiers om de procedures van de studie en/of de gegevens te controleren, zonder de vertrouwelijkheid te schenden. Dit kan enkel binnen de grenzen die door de betreffende wetten zijn toegestaan. Door het toestemmingsformulier, na voorafgaande uitleg, te ondertekenen stemt u in met deze toegang.
Als u akkoord gaat om aan deze studie deel te nemen, zullen uw persoonlijke en klinische gegevens tijdens deze studie worden verzameld en gecodeerd (hierbij kan men uw gegevens nog terug koppelen naar uw persoonlijk dossier)
Verslagen waarin U wordt geïdentificeerd, zullen niet openlijk beschikbaar zijn. Als de resultaten van de studie worden gepubliceerd, zal uw identiteit vertrouwelijke informatie blijven.

Hoe kan ik deelnemen aan deze studie ?
Deelnemen aan deze studie is kosteloos en bent u akkoord met de informatie, dan vragen wij U het bijgevoegde toestemmingsformulier in te vullen en te ondertekenen.

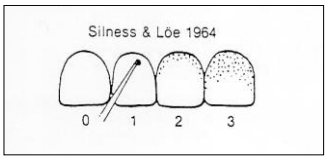
Wilt u verder nog iets weten ?
Hebt u daarnaast nog vragen of wilt u extra informatie over het onderzoek weten, neemt u dan contact met onderzoeker Reda Banon via de afdeling kindertandheelkudne (09/3324036) of per email Reda.elbanoni@ugent.be . Dit onderzoek wordt mede gesuperviseerd door Prof dr. Rita Cauwels.

Reda Banon
Assistent kindertandheelkunde

Prof dr. Rita Cauwels
Kliniekhoofd

11.4 Baseline Oral hygiene status form

Oral hygiene status

Plaque index according to Silness and Löe		
Tooth	Plaque Score 0-3	
16 (55)		
12 (52)		
24 (64)		
36 (75)		
32 (72)		
44 (84)		
	Total =	

DMFT / dmft		
Type		Nr. Of teeth
Permanent	**D**ecayed	
	Missing	
	Filling	
		Total =
Primary	**d**ecayed	
	missing	
	filling	
		Total =

The neighboring tooth

- ☐ **H**ealthy tooth — Tooth to be treated:……
- ☐ **F**illing
- ☐ **C**aries
- ☐ **N**o teeth
- ☐ **O**ther (hypomineralization, SK, etc……)

GHENT UNIVERSITY

Paediatric dentistry

Clinical Evaluation of Tooth Colored Restorations
USPH – Modified Ryge Criteria

Patient name :			OR	Sticker			
UZ File number :							
	Age :						
	Gender : Male / Female						
	Date of evaluation :						
	Name of evaluator :						
	CLINICAL EVALUATION A or B or C						
S.No	CRITERIA	Tooth Nr.:…...	Tooth Nr.:…...	Tooth Nr.:…...	Tooth Nr.:…...	Tooth Nr.:…...	Tooth Nr.:…...
1	Color match						
2	Marginal discoloration						
3	Marginal adaptation						
4	Anatomic form						
5	Gross fracture (restoration)						
6	Tooth fracture						
7	Postoperative sensitivity						
8	Secondary caries (present or not)						
9	Endodontic complications (present or not)						
	RADIOGRAPHIC EVALUATION						
S.No	CRITERIA		Yes/No				
10	Secondary caries						Yes
11	Presence of periradicular radiolucency						Yes
	TO BE FILLED BY THE AUTHOR						
CODE							

Table 11: Included articles with level of evidence (LoE)

Author (Year)	Title	Type	LoE
Mah J. et al. (2017) (77)	Adhesion of S. Mutans Biofilms on Potentially Antimicrobial Dental Composites	In vitro	4
Garcia-godoy F., Morrow B. (2016) (78)	Bioactive Dental Materials Analysis and Evaluation of Dentin Integration	In vitro	4
Brackett M. (2017) (79)	Biocompatibility (MTT Test) of New, Non-Bis-GMA-Based Composites	In vitro	4
Nguyen N. et al. (2015) (59)	Calcium Ion-release From "Bioactive" Dental Restorative Materials	In vitro	4
Hussain S. et al. (2017) (80)	Color Stability of Three Restorative Materials – An In Vitro Study	In vitro	4
Chao W. et al. (2015) (55)	Comparison of Deflection at Break of Four Dental Restorative Materials	In vitro	4
Girn V. et al. (2014) (53)	Comparison of Mechanical Properties of Dental Restorative Material	In vitro	4
Alkhudhairy FI., Ahmad ZH. (2016) (81)	Comparison of Shear Bond Strength and Microleakage of Various Bulk-fill Bioactive Dentin substitutes: An *in vitro* Study	In vitro	4
Ali Alrahlah (2018) (82)	Diametral Tensile Strength, Flexural Strength, and Surface Microhardness of Bioactive Bulk Fill Restorative	In vitro	4
Tewari K. et al. (2016) (83)	Effect of Elevated Temperature on Adhesive Bond Strength to Dentin	In vitro	4
Efes B et al. (2016) (84)	Effects of Two Different Mediums on Different Restorative Materials	In vitro	4
Morrow B. et al. (2017) (56)	Evaluation of pH Fluoride and Calcium Release for Dental Materials	In vitro	4
Jensen M. et al. (2017) (85)	Evaluation of Shear Bond Strength for New Bonding Agent Materials	In vitro	4
Zainab Abdullah Albannawi (2016)	Evaluation of the Antibacterial Effect of Bioactive Dental Restorative Materials: *in vitro* Study	In vitro	4
Pameijer CH. et al. (2015) (45)	Flexural Strength and Flexural Fatigue Properties of Resin-Modified Glass Ionomers	In vitro	4
Slowikowski L. et al. (2014) (57)	Fluoride ion release and recharge over time in three restoratives	In vitro	4
May E. , Donly KJ. (2017) (86)	Fluoride release and re-release from a bioactive restorative material	In vitro	4
Murali S. et al. (2016) (58)	Fluoride Release of Bioactive Restoratives with Bonding Agents	In vitro	4
Epstein N. et al. (2017) (87)	Fluoride Release of Dental Restoratives When Brushed With Fluoridated Toothpaste	In vitro	4
Ammar Asali (2016) (46)	Fluoride Release, pH change and Recharge Ability of Different Types of Glass Ionomer Restorative Materials: A Comparative *in Vitro* Study	In vitro	4
Zmener O. et al. (2013) (88)	Marginal bacterial leakage in class I cavities filled with a new resin-modified glass ionomer restorative material	In vitro	4
Ta M. et al. (2017) (89)	Microleakage Evaluation of Elevated Temperatures in Combined Adhesives and Restoratives	In vitro	4
Ta M. et al. (2015) (90)	Microleakage Evaluation of Elevated Temperatures in Dental Restoratives	In vitro	4
Cannavo M. et al. (2014) (91)	Microleakage of Dental Bulk Fill, Conventional, and Self-adhesive Composites	In vitro	4

Kulkarni P. et al. (2017) (92)	Microleakage Under Class II Restorations Restored With Bulk-fill Materials	In vitro	4
Pameijer CH. , Zmener O. (2011) (44)	Histopathological Evaluation of a RMGI cement, auto and light cured, used as a luting agent – A subhuman primate study	Animal study	4
Pulpdent (47)	pH dependence on the phosphate release of Activa ionic materials	In vitro	4
Lindsey A. et al. (2016) (93)	Profilometry Based Composite Abrasion Using Different Current Dentifrices	In vitro	4
Sharp H. et al. (2016) (94)	Profilometry Based Composite-Enamel Margin Interface Abrasion with Current Dentifrices	In vitro	4
John C Comisi (2017) (95)	Restoring Damaged Tooth Structure with a Novel Resilient Bioactive Restorative Material	Case report	4
Parks H et al. (2016) (96)	Staining and Whitening Products Induce Color Changes of Multiple Composites	In vitro	4
Chao W. et al. (2016) (60)	Surface Deposition Analysis of Bioactive Restorative Material and Cement	In vitro	4
Pulpdent (48)	Water absorption and solubility of restorative materials	In vitro	4
John Burgess (2014) (61)	Wear of a Calcium, Phosphate and Fluoride Releasing Restorative Material	In vitro	4
Garcia-godoy F. , Morrow B. (2015) (62)	Wear Resistance of New ACTIVA Compared to Other Restorative Materials	In vitro	4
John C Comisi (2017) (51)	Bioactive materials clinical choice or clinical necessity?	Case report	4
Theodore P. Croll et al. (2015) (97)	Dental repair material: A resin modified glass ionomer bioactive ionic resin based composite	Case report	4
Theodore Croll, Nathaniel Lawson (2017) (98)	ACTIVA™ BioACTIVE RESTORATIVE ™ Material in Children and Teens: Examples and 46-month Observations	Case series	4
Todd C. Snyder (2017) (49)	A Review of Direct Restorations, Their Applications, and Possibilities	Review	4
Zhang K. et al. (2017)	Bioactive Dental Composites and Bonding Agents Having Remineralizing and Antibacterial Characteristics	Review	4
McCabe JF (2011) (99)	Smart materials in dentistry	Review	4