Final report

Effect of combined silver diammine fluoride and potassium iodide agents on hypersensitive carious primary teeth: an observational cohort study

ZA Mohamed H. Abudrya, OÄ Dr. Ruth M. Santamaría

Prof. Dr. Christian H. Splieth

Universitätsmedizin Greifswald/Germany

Contents

Table of Contents

1. Summary 2

2. Introduction 3

3. Aim 5

4. Material and methods 5

4.1 Statistical analysis 8

5. Results 9

5.1 Baseline characteristics (participants and teeth) 9

5.2 Hypersensitivity 9

5.3 Caries activity 10

5.4 Children's behavior 12

5.5 Parental satisfaction of the treatment 12

5.6 Complications 13

6. Conclusions 14

7. References 14

1. Summary

This observational cohort study primarily aimed to assess the clinical outcomes hypersensitivity relief and caries arrest after the application of combined silver diammine fluoride and potassium iodide (SDF+KI; Riva Star®, SDI Limited) on hypersensitive carious lesions (ICDAS 5) after a 3-month period. Fifteen 2-5-year-olds (mean age 3.58±0.95) who required a desensitizing treatment of hypersensitive carious lesions were recruited at the Department of Preventive and Pediatric Dentistry of Greifswald/University in Germany. After diagnosing hypersensitivity, teeth were isolated, a dentin sample was obtained for activity testing and SDF+KI was applied. Only one tooth per child was included for the analysis. Clinical variables were recorded at baseline and 3 months after treatment. For statistical comparisons between baseline and follow-up, paired t-test, Wilcoxon signed rank test and McNemar test were used.

Results: The 15 participants (9 boys, 6 girls) had a mean dmft of 8.07±2.79. Out of 15 active carious lesions from baseline, 13 (86.7%) were inactive after 3-months, while 2 (13.3%) remained active (Bjørndal Criteria; $p<0.001$). Regarding hypersensitivity, the pain scores before treatment according to the Visual Analogue Scale were clearly reduced from moderate pain (score 4, n=8; 53.3%; score 5, n=7; 46.7% to mostly no (score 0, n=13; 86.7%) or mild pain (score 2; N=1; 6.7%, $p=0.001$). There was no statistical significant difference in behavior before, during and after treatment. Parental satisfaction was very high (86.7%) and all would choose to have the treatment again, rating their children being either comfortable or very comfortable with SDF/KI treatment (86.7%).

Thus, the combination of SDF+KI contained in Riva Star® capsules had a potent effect in desensitizing and arresting caries in hypersensitive active carious lesions in primary teeth.

This study was partially funded by SDI Limited.

2. Introduction

Dentin hypersensitivity is described as short, sharp pain resulting from exposed dentin in response to external stimuli. These stimuli could be thermal, evaporative, tactile, osmotic, or chemical not attributed to any other dental disease or defect [Holland et al., 1997]. Evidence of dentin hypersensitivity (DH) prevalence in children is scarce. The reviews by Shiau [2012], and Splieth and Tachou [2013] reported ranges between 3 to 73% and 3 to 98 % respectively in adults with higher female incidence in the former study. Several theories have been cited to describe hypersensitivity. However, the hydrodynamic theory proposed by Brannstrom and Astrom [1972] is the most commonly accepted theory [Addy, 1992]. Consequently, detin hypersensitivity could be treated by interrupting neural response for pain stimuli or blocking the exposed dentinal tubules [Cummins, 2009]. The management scope of dentin hypersensitivity ranges from using dentifrices [Bae et al., 2015], fluoride varnishes [Petersson, 2013], resin based adhesives and different agents to occlude opened dentinal tubules or even restorations in the unmanageable cases [Koizumi et al., 2016].

One of the most common reason for the clinical outcomes of dentin hypersensitivity are active caries lesions, especially in Early Childhood Caries (ECC) which is defined as the early onset of caries in young children with often rapid progression, which can eventually result in complete destruction of the primary dentition. Epidemiologically, ECC can be defined as the presence of one or more decayed (non-cavitated or cavitated lesions), missing (due to caries), or filled surfaces in any primary tooth of a child under age of 6 [Machiulskiene et al., 2019]. ECC is becoming a significant health problem, rapidly increasing in prevalence, especially in low- and middle-income regions [WHO, 2016]. In Germany, [Splieth et al., 2009] reported results of regional epidemiological studies in 2009 showing a prevalence between 7.3% and 20.3%. Treatment strategies of ECC ranged from dietary behavior alterations and teeth brushing with fluoride toothpastes [Edelstein, and Ng, 2015] to costly surgeries, thereafter a relapse of decay is not uncommon [Graves et al., 2004]. However, a review in 2013 showed promising results of Silver diamine fluoride (SDF) in arresting caries and further prevention of its progression, especially among children who are too young to undergo conventional treatment [Fung et al., 2013].

Silver fluoride (SF)/Silver diamine fluoride (SDF) have been used as an alternative treatment for caries control and arrest [Peng et al., 2012]. In 2014, SDF was approved by the US Food

and Drug Administration as a treatment for dentinal sensitivity [FDA, 2017] and it is commonly used in several countries for treating dentin hypersensitivity associated to the presence of carious lesions. SDF had been used off-label for caries arrest; however, it was recently recommended in the guidelines of the American Dental Association as caries arresting medicament [Slayton et al., 2018].

A concern to consider about SDF was the black staining of the arrested carious lesions, which may result in undesirable aesthetics [Chu et al., 2002]. Despite this concern, most parents preferred this option to advanced behavioral techniques as general anesthesia [Crystal et al., 2017]. Applying a saturated solution of potassium iodide (KI) immediately after silver fluoride application was claimed to minimize the staining of dentin caries while the caries arresting effect of silver fluoride is unaffected [Knight et al., 2006]. This is probably due to the reaction of iodide ions from the KI solution with the excess silver ions from the silver fluoride solution thus forming a precipitate of silver iodide. Moreover, it was showed that dentine permeability could be reduced if potassium iodide was applied after a fluoride containing silver diamine solution, consequently reducing dentin hypersensitivity [Knight et al., 2005]. Hamama [Hamama et al., 2015] and Koizumi [Koizumi et al., 2016] showed positive results regarding the desensitizing and caries arrest effect using a combined silver fluoride and potassium iodide agent SDF/KI; Riva Star® (35-40% SDF and a saturated solution of KI).

Several antimicrobial agents like xylitol and fluoride with different range of application methods have been used, with pronounced reductions in S. mutans and S. sobrinus levels. However, this reduction only lasted for weeks to a few months after treatment. The reduction in bacterial colonization was declined when treatment was deferred [Li, and Tanner, 2015]. The potent antimicrobial activity of silver salts had been reported in several studies [Knight et al., 2005; Parolia et al., 2011; Gillam et al., 2001; Amarasena et al., 2010]. The application of a 20 ppm solution of silver nitrate inhibited the growth of Streptococcus mutans and Staphylococcus aureas efficiently [Merika et al., 2006]. This could be ascribed to the high reactivity of silver ions (Ag+) to the phosphorus and sulfur containing proteins of the bacterial cell wall, resulting in destruction of the outer cell membrane and extrusion of the cytoplasm [Greenhill, and Pashley, 1981].

Precise differentiation of dentin hypersensitivity from other pathologies affecting the teeth is fundamental. It might be clinically contradicted with recently performed poor restorations, cracks or fractures, and reversibly or irreversibly inflamed pulp [Addy, 2002; Addy, 2000]

Tactile stimulation of exploratory probe or triple syringe air jets on the exposed surface provokes a response from the patient [Gillam, and Orchardson, 2006]. Quantification of severity of discomfort (pain) in children affected by ECC is problematic, mainly due to the limited communication abilities at this age [Franck et al., 2000]. Descriptive scales using pictures (faces), which pretend to portray the pain intensity (slight, moderate or intense pain) [Holland et al., 1997], or objective visual analogue scales (VAS) have been used to describe how children feel [Gillam, and Orchardson, 2006]. However, main sourcing of information at young ages are their parents/caregivers.

This study was conducted to assess the effect of application of a combined silver fluoride and potassium iodide agent (Riva Star®, SDI Limited) on active hypersensitive carious lesions in primary teeth.

3. Aim

The ultimate aim of this study is to clinically assess the desensitizing and caries arresting effect of a combined silver diammine fluoride and potassium iodide SDF/KI (Riva Star® 35-40% SDF and a saturated solution of KI) on hypersensitive carious lesions (ICDAS 5) in primary teeth after 3 months. In addition, this study also aimed to assess behavior of the participating children before, during and after treatment along with the parental satisfaction of the treatment.

4. Material and methods

A non-randomized sample of 15 consecutive children attending the Department of Preventive and Pediatric Dentistry at the University of Greifswald from (October 2018) to (August 2019) was collected. Moreover, this study is a part in a two-arm study evaluating the efficacy of the standard therapy (fluoride varnish application 22,600 ppm) on hypersensitive carious lesions in primary teeth with a positive vote of the local ethics committee of the Medical Faculty in Greifswald (No. BB 128/18).

Assessment of eligibility was carried out by a single investigator (MHA). In terms of inclusion criteria, only healthy children aged between 2 to 5 years old were selected. Reported hypersensitivity in primary teeth associated with the presence of active carious lesions

(ICDAS 5) were prerequisites for eligibility. Children with previously restored teeth or signs and symptoms of irreversible pulpitis were excluded. A signed informed consent of participation was mandatory before intervention.

The degree of pain severity was quantified by a visual analogue scale (VAS; scores 0-10; Figure 1) [Gillam, and Orchardson, 2006], ranging across a continuum from none (0) to a severe amount of pain (10). On the other hand, carious lesions activity was evaluated using Bjørndal Criteria (0 – 9= sound –missing tooth, Table 1).

Figure 1. Visual Analogue Scale (VAS) with scoring options from 0 to 10.

Table 1. Bjørndal criteria for caries activity and severity assessment

Score	Definition
0	Sound
1	Active lesion in enamel , without cavity (bright surface with brown discoloration)
2	Active cavity in enamel (opaque enamel surface and loss of substance)
3	Active cavity in enamel (bright surface , brown discoloration, wet dentin)
4	Inactive cavity in enamel (bright surface, brown discoloration and loss of substance)
5	Active cavity in enamel/dentin (yellow or light brown discoloration , wet dentin)
6	Inactive cavity in enamel/dentin (dark brown discoloration, hard and dry dentin)
7	Pulpal involvement or root stumps
8	Filled tooth
9	Missing tooth

Children's behavior before, during and after treatment was assessed using Frankl's Scale (Table 2).

Table 2. Frankl Behavior Scale

Score	Scoring	Observed Behavior
1	Definitely positive	Good rapport with the dentist, interested in the dental procedure, laughing and enjoying the situation
2	Positive	Acceptance of treatment; at time cautious, willingness to comply with the dentist, at times with reservation but patient follows the dentist's directions cooperatively
3	Negative	Reluctant to accept treatment; uncooperative, some evidence of negative attitude but not pronounced
4	Definitely negative	Refusal of treatment, crying forcefully, fearful, or any other overt evidence of extreme negativism

Following hypersensitivity pain assessment and obtainment of an informed consent, affected teeth were isolated either with cotton rolls or liquid dam, followed by application of silver diammine fluoride and potassium iodide SDF+KI (Riva Star®, SDI Limited) according to manufacturer's instructions.

The follow up period of this study was 3 months, at which the following outcomes were evaluated:

- Hypersensitivity pain was re-evaluated using the same method (VAS) in the first recruitment visit.
- Carious lesion activity was re-evaluated using the same visual-tactile criteria for caries activity and severity assessment (Bjørndal Criteria).
- Behaviour of children before, during and after treatment using Frankl Scale.
- Parental perception and satisfaction of the treatment using Five-point Likert scale questionnaire.

Besides, parents were also asked if any complications arose after treatment with SDF+KI and if existed, how long the complication lasted to disappearance.

4.1 Statistical analysis

Normality was checked for all variables using plots and tests of normality. Means and standard deviations (SD) were calculated for all quantitative variables, while frequencies and percentages were calculated for categorical variables. Comparing the baseline and follow-up was done using paired t-test when the variable was normally distributed, and Wilcoxon signed rank test when the variable was not normally distributed. McNemar test was used for comparing lesion activity before and after treatment and Friedman test for comparing the children's behavior at 3 different time points (before, during and after treatment). Significance was set at $P < 0.05$. Data was analyzed using IBM SPSS statistical software (version 25).

5. Results

5.1 Baseline characteristics (participants and teeth)

This study included 15 consecutively recruited healthy children (9 males, 6 females) with a mean age of 3.58 ±0.95, and dmft 8.07 ±2.79. Each patient presented with at least one active carious lesion with visible dentin (ICDAS 5) and reported symptoms of hypersensitivity that signalled the need for a desensitizing treatment. The baseline characteristic of the participants and their caries profile are presented in (Table 3).

Age: mean ± SD		3.58 ± 0.95
Gender: n (%)	**Males**	9 (60%)
	Females	6 (40%)
Caries index/tooth (dmft) mean ± SD	**dt**	6.73 ± 2.43
	mt	0.13 ± 0.51
	ft	1.20 ± 1.86
	dmft	8.07 ± 2.79
Caries index/surface (dmfs) mean ± SD	**ds**	18.73 ± 10.48
	ms	0.67 ± 2.58
	fs	4.53 ± 7.62
	dmfs	23.93 ± 14.75

Table 3. Sample characteristics and caries profile (n=15) at baseline

5.2 Hypersensitivity

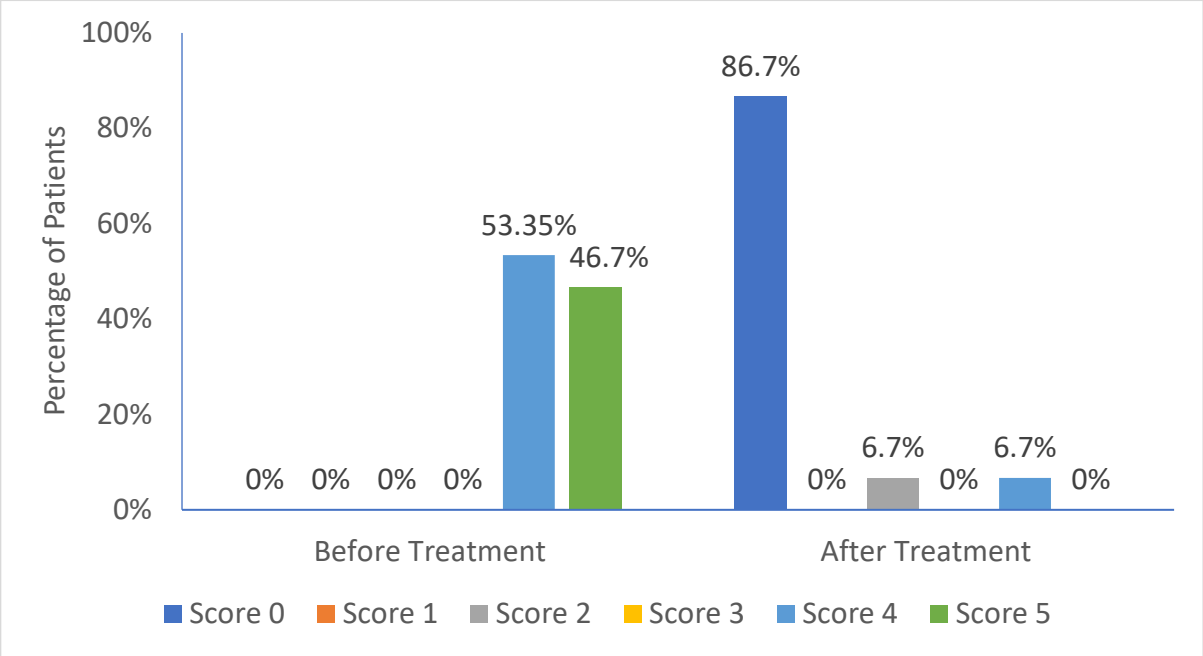
Regarding hypersensitivity pain (Table 4, Figure 2), assessment before treatment showed moderate pain scores on the Visual Analogue Scale (VAS), scores 4 and 5 were reported by 8 (53.3%) and 7 children (46.7%), respectively.

After 3-months, 13 (86.7%) patients' parents reported absence of pain (score 0), 1 (6.7%) reported decrease of pain intensity to a milder pain (score 2) and 1 (6.7%) child's parent reported no change in pain (score 4). Decline in pain scores after treatment was statistically significant (p=0.001).

Table 1. Pain assessment using Visual Analogue Scale (VAS) as reported by parents before and after treatment (*statistically significant at p value <0.05)

Score	Before Treatment	After Treatment
0	0 (0%)	13 (86.6%)
1	0 (0%)	0 (0%)
2	0 (0%)	1 (6.7%)
3	0 (0%)	0 (0%)
4	8 (53.3%)	1 (6.7%)
5	7 (46.7%)	0 (0%)
P Value	0.001*	

Figure 2. Pain assessment using Visual Analogue Scale (VAS) as reported by parents before and after treatment



5.3 Caries activity

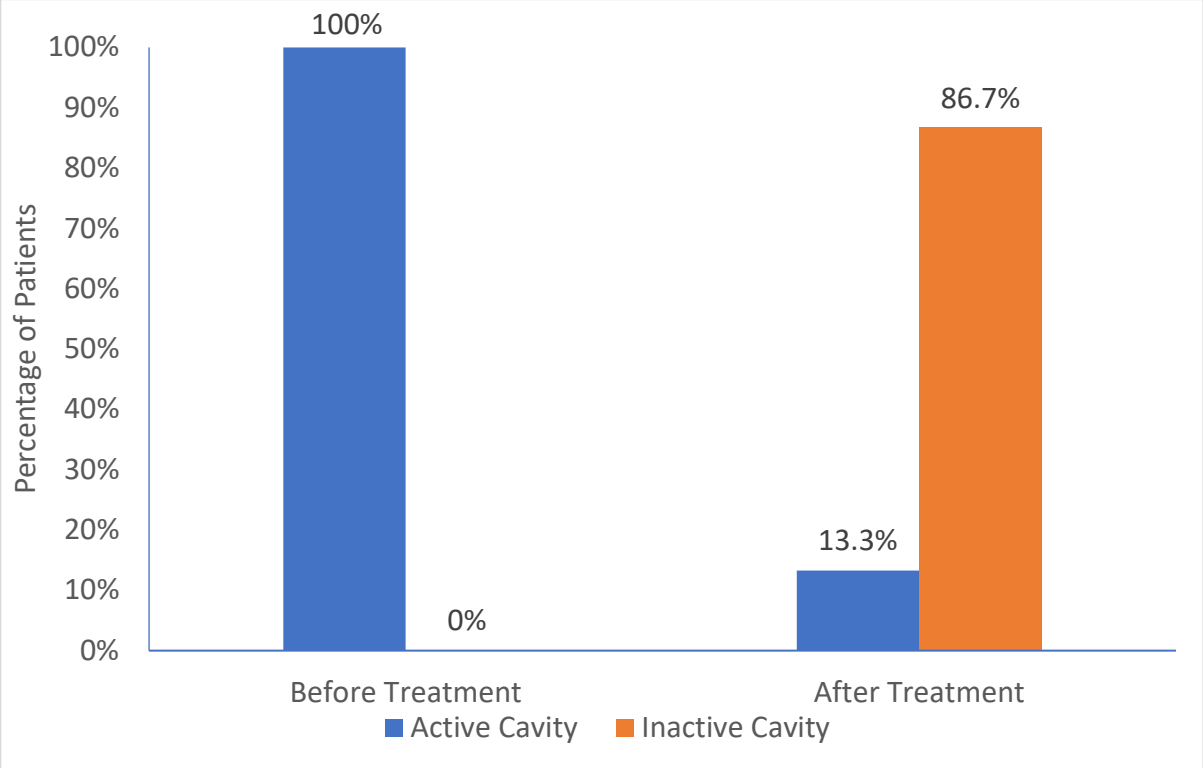
At baseline, 15 (100%) caries lesions with visible dentin (ICDAS 5) in all 15 participants showed visual and tactile features of caries activity during examination and were graded as active cavity in enamel/dentin according to Bjørndal criteria for caries activity and severity assessment. Three months after treatment with SDF/KI, affected teeth were re-examined using the same criteria and 13 (86.7%) out of 15 lesions were classified as inactive cavity in enamel/dentin (Figure 3). Active caries was evident in only 2 (13.3%) lesions at 3-months

follow up. However, the predominance of arrested lesions over the remaining active ones was statistically significant (p<0.001) (Table 5).

Table 5 Activity of carious lesions according to Bjørndal Criteria before and after treatment (*statistically significant)

Score	Before Treatment	After Treatment
Active cavity in enamel/Dentin (Score 5)	15 (100%)	2 (13.3%)
Inactive cavity in enamel/Dentin (Score 6)	0 (0%)	13 (86.7%)
P Value	<0.001*	

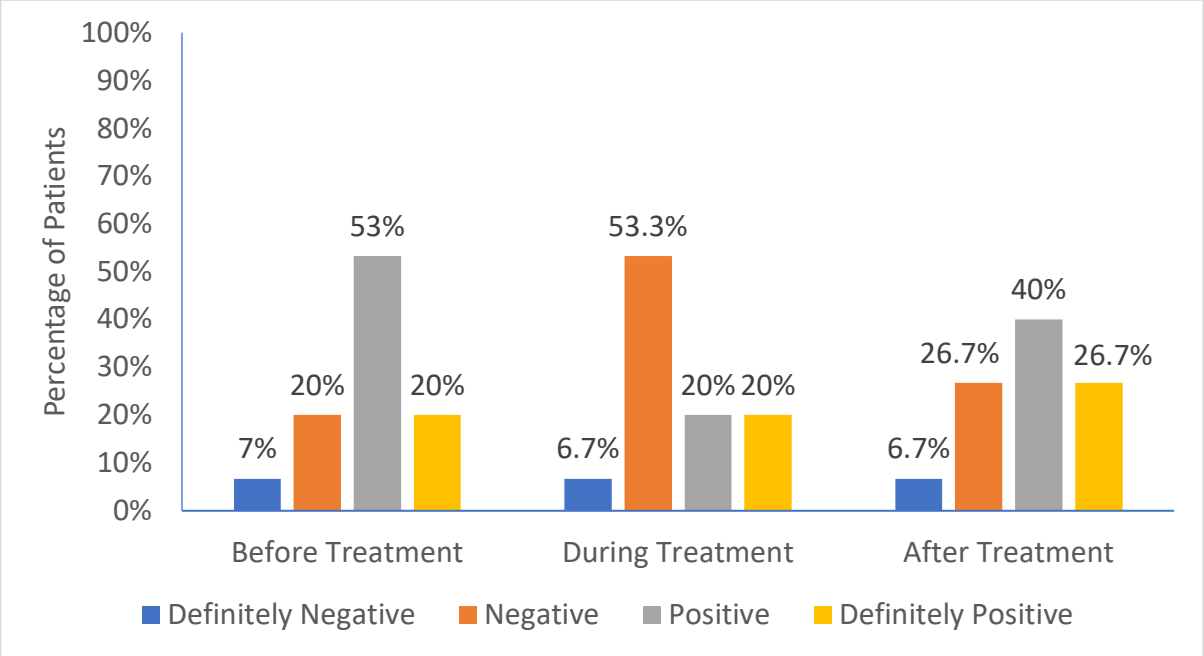
Figure 3. Activity of carious lesions according to Bjorndal Criteria before and after treatment.



5.4 Children's behavior

Prior to treatment the majority of the participants showed positive 8 (53.3%) or definitely positive 3 (20%) behaviour, while 3 (20%) children showed negative behaviour. Negative behaviour during treatment was noticed among 8 (53.3%) children while 6 (40%) children equally showed a rating of either positive or definitely positive behaviour. Only one patient (6.7%) was rated by the treating dentist as having a 'definitely negative' behaviour before, during and after treatment. Post-operative behaviour was mainly on the positive side, with 6 (40%) children rated as positive and 4 (26.7%) as definitely positive. Only 2 (26.7%) participants sustained a negative behaviour after treatment. However, significant differences were not found between behaviour ratings before, during and after treatment (p=0.07) (Figure 4).

Figure 4. Behavior using Frankl Scale before, during and after treatment.

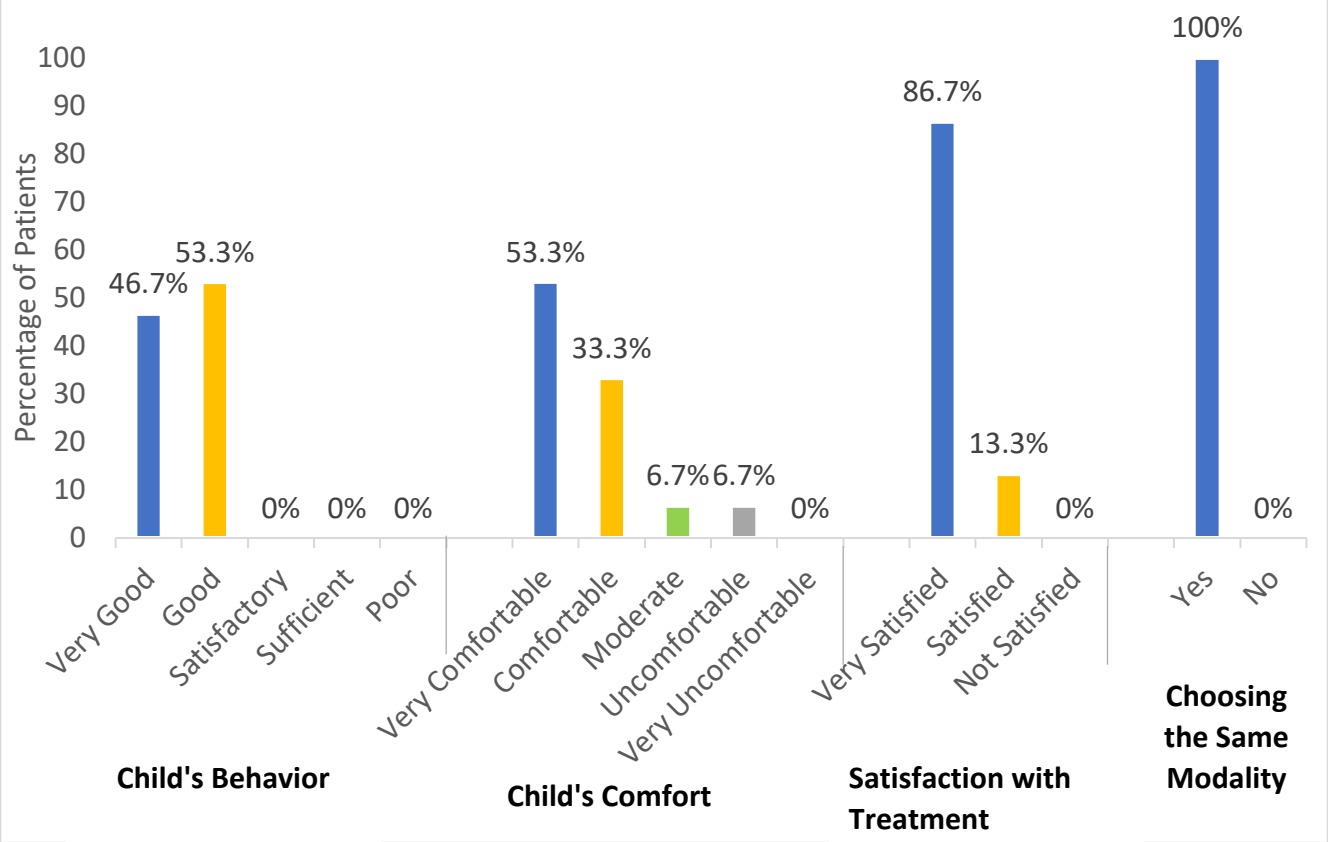


5.5 Parental satisfaction of the treatment

The great majority of parents (86.7%) were very satisfied with the procedure and all would choose to have the treatment again. Regarding the child's comfort, only 1 (6.7%) of the participants parents rated their child as uncomfortable, while most parents 13 (86.7%) rated their children either comfortable or very comfortable with SDF/KI treatment. Moderate

comfort was reported by 1 (6.7%) parent. The child's behaviour from a parental view was considered either 'very good' or 'good' among all the parents (Figure 5).

Figure 5. Parent's perception about the procedure and treatment modality.



5.6 Complications

No serious procedural or post-operative complications were recorded and all adverse events seen during or after the procedure were reversible.

In 5 (33.3%) children, parents reported a post-operative discoloration on the lips/tongue that disappeared within 2-3 days.

6. Conclusions

At the 3-months follow-up, the analyzed data from this study sample unveiled the fast-acting positive effect of combined silver diammine fluoride and potassium iodide SDF+KI (Riva Star®, SDI Limited) treatment on hypersensitive carious lesions with visible dentin (ICDAS 5) in primary dentition. Accounting the statistical significant difference found in hypersensitivity pain decline and caries arrest among the study participants, SDF/KI can be considered a valid desensitizer with caries-arresting potential. Moreover, the high parental satisfaction after 3 months of the treatment demonstrated the importance of a low-risk, non-invasive caries therapy over esthetic demands. However, consenting the parents to the esthetic drawback of the treatment is essential, but it has to be outweigh with the alternatives which is often restricted to the more risky and invasive treatment under general anesthesia for small, uncooperative children. Ultimately, treatment with SDF+KI had no influence over the child's behavior within this study's sample.

7. References

Addy M: Clinical aspects of dentine hypersensitivity [Internet]. . Proc Finn Dent Soc 1992;88 Suppl 1:23–30.

Addy M: Dentine hypersensitivity: Definition, prevalence, distribution and etiology. In: Addy M, Embery G, Edgar WM, Orchardson R, editors. Tooth wear and sensitivity: Clinical advances in restorative dentistry. London: Martin Dunitz;. 2000;239–248.

Addy M: Dentine hypersensitivity: New perspectives on an old problem. Int Dent J 2002; DOI: 10.1002/j.1875-595x.2002.tb00936.x

Amarasena N, Spencer J, Ou Y, Brennan D: Dentine hypersensitivity - Australian dentists' perspective. Aust Dent J 2010; DOI: 10.1111/j.1834-7819.2010.01223.x

Bae JH, Kim YK, Myung SK: Desensitizing toothpaste versus placebo for dentin hypersensitivity: A systematic review and meta-analysis. J Clin Periodontol 2015; DOI: 10.1111/jcpe.12347

Brannstrom M, Astrom A: The hydrodynamics of the dentine; its possible relationship to dentinal pain [Internet]. . Int Dent J 1972;22:219–227.

Chu CH, Lo ECM, Lin HC: Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children. J Dent Res 2002;81:767–70.

Crystal YO, Janal MN, Hamilton DS, Niederman R: Parental perceptions and acceptance of silver diamine fluoride staining. J Am Dent Assoc 2017;148:510-518 e4.

Cummins D: Dentin hypersensitivity: from diagnosis to a breakthrough therapy for everyday sensitivity relief [Internet]. . J Clin Dent 2009;20:1–9.

Edelstein BL, Ng MW: Chronic Disease Management Strategies of Early Childhood Caries: Support from the Medical and Dental Literature [Internet]. . Pediatr Dent 2015;37:281–287.

FDA: Food and Drug Administration. Diammine Silver Fluoride Dental Hypersensitivity Varnish. 510(k) Premarket Notification; 2017. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K102973. Accessed 2020 Jan 20. 2017;

Franck LS, Greenberg CS, Stevens B: Pain assessment in infants and children. Pediatr Clin North Am 2000; DOI: 10.1016/S0031-3955(05)70222-4

Fung M, Wong M, Lo E, Chu C: Arresting Early Childhood Caries with Silver Diamine Fluoride-A Literature Review. J Oral Hyg Heal 2013; DOI: 10.4172/2332-0702.1000117

Gillam DG, Mordan NJ, Sinodinou AD, Tang JY, Knowles JC, Gibson IR: The effects of oxalate-containing products on the exposed dentine surface: An SEM investigation. J Oral Rehabil 2001; DOI: 10.1111/j.1365-2842.2001.00775.x

Gillam DG, Orchardson R: Advances in the treatment of root dentine sensitivity: mechanisms and treatment principles. Endod Top 2006; DOI: 10.1111/j.1601-1546.2006.00209.x

Graves CE, Berkowitz RJ, Proskin HM, Chase I, Weinstein P, Billings R: Clinical outcomes for early childhood caries: Influence of aggressive dental surgery. J Dent Child 2004;

Greenhill JD, Pashley DH: The Effects of Desensitizing Agents on the Hydraulic Conductance of Human Dentin in vitro. J Dent Res 1981; DOI: 10.1177/00220345810600030401

Hamama HH, Yiu CK, Burrow MF: Effect of silver diamine fluoride and potassium iodide on residual bacteria in dentinal tubules. Aust Dent J 2015;60:80–87.

Holland GR, Narhi MN, Addy M, Gangarosa L, Orchardson R: Guidelines for the design and conduct of clinical trials on dentine hypersensitivity. J Clin Periodontol 1997;24:808–813.

Knight GM, McIntyre JM, Craig GG, Mulyani: Ion uptake into demineralized dentine from glass ionomer cement following pretreatment with silver fluoride and potassium iodide. Aust Dent J 2006; DOI: 10.1111/j.1834-7819.2006.tb00435.x

Knight GM, McIntyre JM, Craig GG, Mulyani, Zilm PS, Gully NJ: An in vitro model to measure the effect of a silver fluoride and potassium iodide treatment on the permeability of demineralized dentine to Streptococcus mutans. Aust Dent J 2005; DOI: 10.1111/j.1834-7819.2005.tb00367.x

Koizumi H, Hamama HH, Burrow MF: Effect of a silver diamine fluoride and potassium iodide-based desensitizing and cavity cleaning agent on bond strength to dentine. Int J Adhes Adhes 2016; DOI: 10.1016/j.ijadhadh.2016.02.008

Li Y, Tanner A: Effect of antimicrobial interventions on the oral microbiota associated with early childhood caries; in : Pediatric Dentistry. 2015.

Machiulskiene V, Campus G, Carvalho JC, Dige I, Ekstrand KR, Jablonski-Momeni A, et al.: Terminology of Dental Caries and Dental Caries Management: Consensus Report of a Workshop Organized by ORCA and Cariology Research Group of IADR. Caries Res 2019; DOI: 10.1159/000503309

Merika K, HeftitArthur F, Preshaw PM: Comparison of two topical treatments for dentine sensitivity. Eur J Prosthodont Restor Dent 2006;

Parolia A, Kundabala M, Mohan M: Management of dentinal hypersensitivity: a review. J Calif Dent Assoc 2011;

Peng JJY, Botelho MG, Matinlinna JP: Silver compounds used in dentistry for caries management: A review. J Dent 2012; DOI: 10.1016/j.jdent.2012.03.009

Petersson LG: The role of fluoride in the preventive management of dentin hypersensitivity and root caries. Clin Oral Investig 2013;17:63–71.

Shiau HJ: Dentin hypersensitivity. J Evid Based Dent Pract 2012; DOI: 10.1016/S1532-3382(12)70043-X

Slayton RL, Urquhart O, Araujo MWB, Fontana M, Guzmán-Armstrong S, Nascimento MM, et al.: Evidence-based clinical practice guideline on nonrestorative treatments for carious lesions: A report from the American Dental Association. J Am Dent Assoc 2018; DOI: 10.1016/j.adaj.2018.07.002

Splieth CH, Tachou A: Epidemiology of dentin hypersensitivity. Clin Oral Investig 2013;17 Suppl 1:S3-8.

Splieth CH, Treuner A, Berndt C: Orale Gesundheit im Kleinkindalter. Pravention und Gesundheitsforderung 2009; DOI: 10.1007/s11553-009-0167-z

WHO: WHO Expert Consultation on Public Health Intervention against Early Childhood Caries: report of a meeting, Bangkok, Thailand, 26–28 January 2016. Geneva: World Health Organization; 2017 (WHO/NMH/PND/17.1). Licence: CC BY-NC-SA 3.0 IGO. 2016;