

A systematic review of the relationship between Liquid medicines and Dental caries in chronically ill children

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Abstract

Background: A systematic review of studies was conducted to update evidence on the association between dental caries experience and use of liquid medication in chronically ill children on long term basis.

Methods: Data sources included PubMed, PMC electronic databases using the National Library of Medicine’s Medical Subject Heading (MeSH) terms like sucrose, dental caries, child and chronic disease from January 1977- January 2020. Quality of evidence was assessed using Joanna Briggs Institute Critical Appraisal Tools.

Results: From 25 papers identified, 7 studies were eligible – all were cross sectional in nature. None was excluded on the basis of quality. The results of this systematic review

showed mixed findings of association between sucrose in LOM and dental caries. Four reports showed positive association, two studies reviewed found no association while 1 found mixed results.

Conclusion: Although the precise nature of these associations remains unclear, it is highly possible that sucrose act as additive risk factor in the development of caries in chronically ill children on long term LOM as the studies providing negative association are retrospective studies with weak evidence due to presence of response and selection bias. Integration of oral health with Non-Communicable Diseases (Anemia, Malnutrition, Nephrotic Syndrome, epilepsy, congenital heart disease, asthma etc) prevention program is required by the Pediatrician so that

the effect of disease or illness and intake of sweetened medicines can be overcome. Preventive and conservative dental treatment should be given priority in these types of patients.

Keywords: sucrose, dental caries, chronic disease

Introduction

Incorporation of sugars, particularly sucrose into medicines, primarily to improve palatability, is of great concern [1]. These are the additional source of sugar for children suffering from epilepsy [2] neurological disorder [3], respiratory problems [4], recurrent otitis media [5] etc. Several plaque ph [6-9] and observational studies [2, 3, 5] have provided evidence relating liquid oral medication and dental caries. Historically, many independent expert and consensus reports have concluded that sugar particularly sucrose is the most important factor in the development of dental caries in chronically ill children. However, systematic reviews of the evidence have not yet been developed on the same. The objectives were to systematically review all available published data relating to the dental caries experience in chronically ill children on long term LOM.

Method

There is inconclusive evidence suggesting a possible association between children on long term LOM suffering from chronic illness and increased risk of caries. The authors conducted a systematic review with an aim to synthesize the evidence on the relationship between dental caries experience and use of medicine in chronically ill children on long term basis.

Selection criteria for the studies in this review

Type of Studies: Authors included Cross sectional studies investigating association between dental caries, chronic illness and long term liquid oral medication. We excluded case control studies, in vitro studies and review articles. Abstracts and unpublished studies were not included.

Type of Participants: We included studies that involved children chronically ill and suffering from any chronic condition, which did or did not have a history of carious lesions and were on long term LOM from 3 months or more. Children of all age groups were included.

Type of Outcome Measures: Dental caries outcomes included were: caries prevalence measured as DMF Index, DMFT, dmft, DMFS, dmfs, deft, dft, or comparisons between caries and no caries or higher caries vs. lower caries in chronically ill children on Long term liquid oral medication. We defined “Long term” as for more than three months [10]. We defined “chronically ill” as duration exceeds three months [10].

Search Mode for the Identification of Studies: A systematic approach was adopted using electronic databases to search the literature. We searched the PubMed, PMC electronic databases using the National Library of Medicine’s Medical Subject Heading (MeSH) terms like sucrose, dental caries, child and chronic disease from January 1977- January 2017. Further research was conducted on the internet via search engines like Google Scholar and Index Copernicus. Backward and forward citation chasing was also done to expand our search and to ensure that we have not omitted the relevant studies. To enhance the search criteria hand searching and cross referencing was also done. We excluded those studies which were not in English language.

Data Collection and Analysis

Selection of Studies: It was a two stage screening method. In the first stage, 2 reviewers (A.G., R.N.) independently assessed the titles and abstracts of all retrieved references. An inclusive criterion was used and then the reviewers disagreed on the eligibility status for a particular reference, and resolved the disagreement at the full-text screening stage. In the second stage, 2 reviewers independently screened the full text of all the eligible studies. Eligibility

criteria were applied when reading the full text. Differences between reviewer's results were resolved by means of discussion. When consensus was obscure, a third reviewer (H.K), acting as an arbiter, decided final eligibility.

Data Extraction and Management: Two reviewers (A.G., R.N) independently extracted data from all the included studies. The form included instructions to extract the main characteristics of the studies, including the type of study design (cross sectional), medical problems (chronically ill children), duration of use of medication (for 3 months or more), and the outcome measured (dental caries). When these reviewers identified any discrepancies that they were unable to elucidate, a third reviewer (H.K) acted as arbiter.

Assessment of Quality of Evidence: Joanna Briggs Institute Critical Appraisal Tools ^[11] was used to assess the quality of the body of evidence in relation to each of the review questions. The JBI system rates the overall quality of evidence by taking into consideration factors including: inclusion criteria, study subjects and study setting, use of standard criteria, identifying confounding factors and strategies to deal with the same, outcome measured and use of appropriate statistical analysis. Overall Appraisal includes inclusion or exclusion of article. The quality of the evidence was categorized as good, fair and poor.

Results

Results of the Search: The Figure 1 presents a flow diagram for the searches and identification of included studies. From all databases combined, 25 search hits were found. After further screening, 18 papers were excluded that did not meet the inclusion criteria. The remaining 7 full papers were assessed for inclusion/exclusion by two reviewers and thereafter included,

Characteristics of the Included Studies: We included 7 articles ^[2,3,5,12-15] published from 1977 through 2017, whose investigators had reported data related to dental caries experience association with use of liquid oral medication on long term in chronically ill children.

The majority of studies identified were cross sectional in nature which was included. Table 1 provide an overview of the included studies and the characteristics of the populations which investigators described as including children aged 9 months to 17 years. Only one study identified was case control ^[16], others were in vitro studies ^[17] and review articles ^[10] which were excluded (Table 2). No RCTs were identified.

Effect of Liquid Oral Medication: The analysis included 7 cross sectional studies (Table 1). None was excluded on the basis of quality. The results of this systematic review showed mixed findings of association between sucrose in LOM and dental caries. By our criteria, there was only four reports ^[2, 12, 13, 15] that showed a strong relationship between the experience of dental caries and intake of liquid oral medicine on long term basis for 9 months to 17 years of age. In relative terms, the patients who were on LOM had more chances of developing dental caries than those not on LOM. 2 studies reviewed found no association ^[3, 14] while 1 found mixed results ^[5].

Discussion

Disparity in findings was seen in different studies. We suggest that dental caries and LOM are related in a nonlinear fashion with more dental caries occurring in individuals with either children on LOM or not. Furthermore we suggest that methodological factors, including sample demographics, the sensitivity of the dental examination, and the nature of the data analyses especially detecting and controlling for confounding factors influence whether or not the association is detected.

The evidence supporting an inverse relationship between dental caries and LOM comes from retrospective studies done in developing country Brazil on patient suffering from neuropsychomotor disorder^[3] and congenital heart disease^[13]. In spite of continuous use of medication in 72% of the children suffering from neuropsychomotor disorders the association found was weak^[3]. On the other hand, in the second study it led to a statistically higher “missing” component ($p=0.0419$)^[13]. The use of sucrose in medication can explain this finding. Socioeconomic conditions (i.e. Lower socioeconomic status) clearly impact the development of caries and need to be understood. This could also be a contributory factor for the higher missing component. The desirability of getting oral disease treated at its incipient stage is less in people of lower socioeconomic status. A multitude of factors such as poor oral hygiene, low parental education level, poor feeding habits, limited access and affordability to services and support, associated with low SES, are also associated with higher missing component. This pattern may be also due to the severity of dental disease or child’s medical condition encouraging the decision to extract, rather than restore the teeth, if child’s health was seriously threatened by dental infection. Extractions can be predominantly high in mentally and physically compromised children requiring long term medication where the management by routine restorative procedure become difficult. So these confounding factors need to be addressed and controlled for finding the actual association between LOM and dental caries.

Two studies^[5, 14] included in this review found no association between dental caries and sugar in LOM. We have recommended that several methodological factors may have contributed to these findings including: 1) collection of the data from medical and dental records of children which may have the possibility that there may be

absence of important information or incorrect registers of it in the records; 2) several risk factors may contribute to the occurrence of disease therefore logistic regression can be applied to detect the actual association; 3) its observational design that does not allow inferences based on causality.

The studies that support a positive association between dental caries and sugar in LOM include those done by Roberts and Roberts (1979)^[12] who examined children taking syrup medication regularly at least for six months primarily for urinary tract infections, epilepsy and asthma. Both antimicrobial and non anti microbial medicine were involved. The chronically ill children had a mean defs of 5.6, significantly higher than a control group (1.3 defs) on tablet form of medication or not at all on any form of medication. Similarly a study considering both antimicrobial and non anti-microbial medicine reported more caries of deciduous anterior teeth in children on LOM for 1 or more year when the other contributing variables were controlled^[13]. Sahgal J et al (2002)^[15] reported highly significant difference in level of caries in 2-6 year age and for 6-12 year old children. The grade of lesion (percentage) also increased with increase in duration of LOM. A study conducted on epileptic children found 2.55 times increased caries risk in those on Liquid Oral Medicine on long term (prevalence= 76.1%) than those with other forms of medications (prevalence= 55.6%)^[2]. Analysis of data from all of these above identified studies of children detected a statistically significant positive relationship between LOM and levels of caries. The most important barrier found for good oral health is lack of awareness and knowledge. The parents of the children are not relevant with the fact that liquid oral medication can lead to dental caries.

It is not surprising to find the age adjusted odds ratios for caries experience as opposed to no caries experience in

deciduous dentition 1.27 (95%CI: 0.55-2.97) in the study children on LOM versus their siblings ^[13]. The use of medicine becomes an additive factor for the increase in level of dental caries. The need to use sucrose as a sweetening agent in liquid medicines, particularly in paediatric medical practices, should be seriously questioned and reassessed. The use of non-fermentable sweetening agents like xylitol should be promoted. Most importantly, the children who are chronically ill, dental disease can be prevented by providing them preventive and conservative dental care and making sure that liquid medicine is not given in a sucrose base.

One of the seven study included in the systematic review found mixed result ^[5]. The effect of syrup medication on recurrent otitis media was seen on dental health. With the use of antibacterial syrup medication significant decline in dental caries was found at first but with the use of antihistamines and discontinuation of antibacterial syrup medication accelerated form of new carious lesion took place. An antimicrobial syrup medication which may act as anticariogenic have over rided the effect of sucrose provided it has strong anti streptococcal spectrum. But in case of nonantimicrobial medication instead, the cariogenic effect of the syrup medication may override the cariostatic effect. Therefore as a result of prolonged medication, it can lead to new carious lesion.

Integration of oral health in Non- Communicable Diseases (Anaemia, Malnutrition, Nephrotic Syndrome, Epilepsy, Congenital heart disease, Asthma etc) prevention program is required by the Paediatrician so that the effect of disease of disease or illness and intake of sweetened medicines can be overcome ^[18,19]. Several recommendations can be proposed based on our findings for future research in this field:

1. When screening for dental caries, incipient caries should also be included in the caries measure, and the

diagnostic criteria used by all researchers should be same to enable comparisons to be made across studies. Despite of the fact that many attempts have been made to standardize caries assessment for research purposes since 2002 *e.g.*, International Caries Detection and Assessment System (ICDAS)] considerable disparity in diagnostic criteria still exists.

2. To permit some level of comparison to be made across studies, it would be useful that the effect of antimicrobial medication if used should be considered and assessed separately.

3. The possibility of a non-linear association between dental caries and sugar in LOM should be considered, as there are multitude of factors causing dental caries and appropriate analyses performed when testing the relationship.

4. The ability of analytical cross-sectional studies to draw valid conclusions about association between outcomes and risk factors is limited as both are measured simultaneously. Therefore it becomes very difficult to measure, which came first weather the disease or the exposure, so causation should always be confirmed by more precise studies. There is also high risk of recall bias as the collection of information about risk factors is retrospective.

5. Given the impact of other factors such as education level, oral hygiene practices, socioeconomic status, diet, feeding practices and so on, on the development of dental caries as found across studies, a focus on these influences is warranted. These factors should be controlled while calculating the effect of sucrose in LOM on dental caries in chronically ill children.

Conclusion

There is evidence that intake of medicine in chronically ill children may be associated or not associated with development of dental caries. The studies providing

negative association are retrospective studies with weak evidence. There are high chances of response and selection bias in these types of studies. Although the precise nature of these associations remains unclear, it is highly possible that sucrose act as additive risk factor in the development of caries in chronically ill children on long term LOM. Evidence supports the proposal of strategies to target sucrose based medicine. Specific attention should be given to develop alternatives to these sucrose based medicine like use of xylitol. Preventive and conservative dental treatment should be given priority in these types of patients so that the effect of disease or illness and intake of sweetened medicines can be overcome.

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Legend Figure and Tables

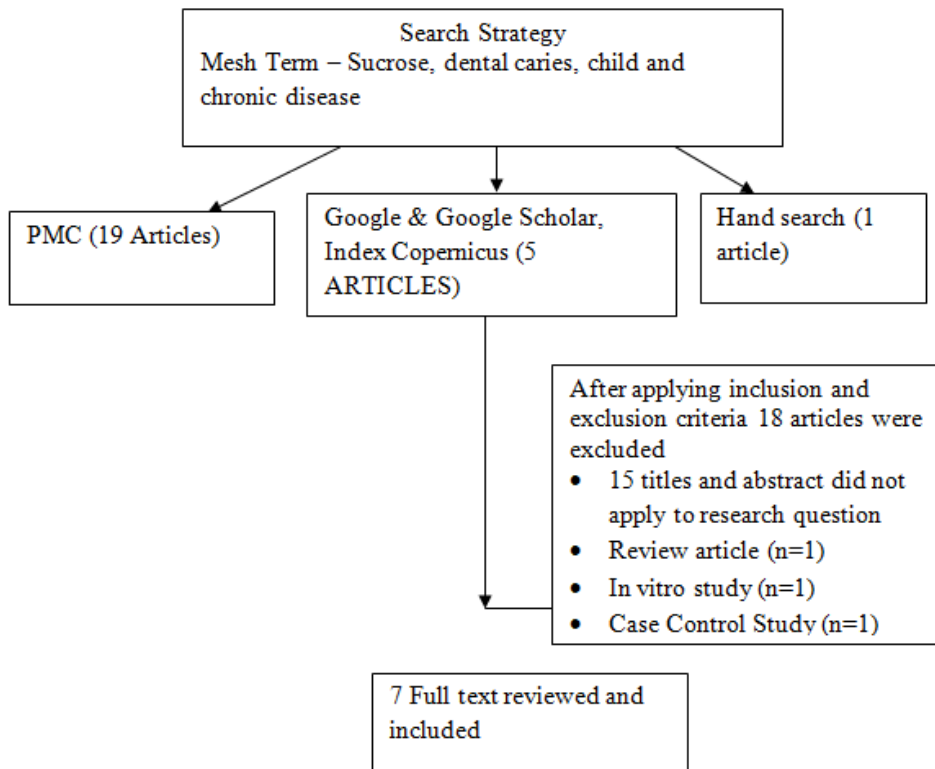


Figure 1: Flowchart of searches

Table 1: Characteristics of the Included Studies

| Sr. No. | Author | Type of study | No. of Patient | Age group | Medical problems | Duration of use of medication | Outcome measured | Findings |
|---------|----------------------------------|-----------------------|---------------------------------------|------------------------------|---|-------------------------------|---|---|
| 1. | Roberts IF and Roberts GJ (1979) | Cross sectional study | Study Group: 44 Control Group: 47 | between 9 months and 6 years | Nervous System (mostly with fits) Respiratory System (mostly asthma) Urinary Tract infection, Others | At least Six Months | Decayed Missing Filled Surfaces Index | Total carious score [DEF(S)] Study Group: 5.55 Control Group: 1.26 p value: 0.02 |
| 2. | Karjalainen S et al (1992) | Cross sectional study | Study Group: 64 Control Group: 212 | 6-8 year | Recurrent otitis media | More than six months | WHO criteria of dmft/DMF | The dmft of the adenoidectomized children at the age of 3 years (mean \pm SEM: 0.5 ± 0.1) which was significantly ($p < 0.005$) lower than that of the controls (1.1 ± 0.2). At the age of 4 years the difference was still significant ($p < 0.01$) but disappeared thereafter. |
| 3. | Maguire A et al (1996) | Cross sectional study | Study Group: 94 Control Group: 92 | 2-17 years | Epilepsy, cystic fibrosis, chronic renal failure, asthma, recurrent urinary tract infections, cardiac | ≥ 1 year | dmft/DMFT dmfs/DMFS | differences in the proportions of caries experience in anterior and posterior teeth: study group v/s |

| | | | | | | | | |
|----|---------------------------|-----------------------|--------------------------------------|-------------------------|---|---|--|--|
| | | | | | disease and chronic constipation. | | | control group; p =0.0008 HS |
| 4. | Sahgal J et al (2002) | Cross sectional study | Study Group: 51 Control Group: 54 | 2-6 years 6-13 years | Recurrent URTI, LRTI T.B. meningitis, pulmonary T.B., cerebral palsy, rheumatic heart disease, enteric fever, persistent cough, non specific post diarrhoeal colitis, mitral regurgitation, gastroenteritis, hypoglycaemia, idiopathic Epilepsy and jaundice. | for 3 months or longer in the past and at least for 1 month continuously at the time of examination | DMFT & S for permanent and dmft & s for primary dentition | For age 2-6 Years: dmft:p<0.001 HS For age 6-13Years: DMFT:p<0.05 sig For age 2-6 Years: dmfs:p<0.01 sig For age 6-13Years: DMFS:p NS |
| 5. | Pimentel ELC et al (2013) | Cross sectional study | 91 patients | 3-5 years | Congenital heart disease | Chronic use of medicine Exact period not given | WHO criteria for deciduous teeth, i.e. the dmft (the sum of decayed teeth, teeth missing because of caries, and filled teeth) index. Secondary outcome: | |

| | | | | | | | | |
|----|-------------------------------|-----------------------------|---|-------------------------------|--|-----------------------|---|--|
| | | | | | | | Association b/w dental caries and daily use of medicine in CHD patient | |
| 6. | Hartwig AD et al (2016) | Cross sectional study | 75 patients | Up to 12 years old | Neuropsychomotor disorders which include: Cerebral palsy (33.9%), Down syndrome (26.3%), and the intellectual disability (10.2%). Other Disabilities (29.6%): West syndrome, Williams syndrome, autism, and cerebral atrophy | More than 6 months | WHO Criteria of dmft / DMFT | dmft / DMFT Study Group= 3.33 Control Group= 3.00 (p-value= 0.686) |
| 7. | Goyal A et al (2017) | Cross sectional study | Study Group: 84 Control Group: 124 | mean age: 5.38 years | Epileptic | >3 months | dmft and dmfs 1944; DMFT and DMFS 1938 | OR: 2.55, 95% CI (2.37-4.15) p=0.000, HS). Caries prevalence study group: (76.1%) control group: (55.6%). |

SS: statistically significant; HS: Highly Significant; WHO: World Health Organization; SEM: Standard error of the mean; DEF(S): Decayed Extracted/Missing Filled Surfaces; DMFT: Decayed Missing Filled Teeth; dmft: decayed missing filled teeth; OR: Odds Ratio; CI: Confidence Interval

Table 2: Details of Two Papers Identified From Literature Review and Reason For Exclusion

| S. No. | Authors | Title | Journal | Year | Type of research | Reason for exclusion |
|--------|--------------------------------------|--|---|------|--------------------|----------------------|
| 1. | Tupalli AR, Satish B, and Nagaraju B | Evaluation of the Erosive Potential of Various Pediatric Liquid Medicaments: An in-vitro Study | Journal of International Oral Health | 2014 | Original | In-vitro study |
| 2. | Foster H and Fitzgerald J | Dental disease in children with chronic illness | Arch Dis Child | 2005 | Review | Review |
| 3. | Stecksen-Blicksi C et al | Dental caries experience in children with congenital heart disease: a case-control study. | International Journal of Paediatric Dentistry | 2004 | Case control study | Case control |

Table 3: Table Quality Assessment of Included Studies Using Joanna Briggs Institute Critical Appraisal Tools

| Factors included | Roberts IF and Roberts GJ (1979) | Karjalainen S et al (1992) | Maguire A et al (1996) | Sahgal J et al (2002) | Pimentel ELC et al (2013) | Hartwig AD et al (2016) | Goyal A et al (2017) |
|---|----------------------------------|----------------------------|------------------------|-----------------------|---------------------------|-------------------------|----------------------|
| Were the criteria for inclusion in the sample clearly defined | Yes | Yes | Yes | Unclear | Yes | Yes | Yes |
| Were the study subjects and the setting described in detail | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Was the exposure measured in a valid and reliable way | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Were objective, standard criteria used for measurement of the condition | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Were confounding factors identified | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

| | | | | | | | |
|---|-----|-----|-----|---------|-----|-----|-----|
| Were strategies to deal with confounding factors stated | Yes | Yes | Yes | Unclear | Yes | No | Yes |
| Were the outcomes measured in a valid and reliable way | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Was appropriate statistical analysis used | No | No | Yes | No | No | No | No |