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Split-mouth design in Paediatric Dentistry clinical trials

ABSTRACT

Aim *The aim of this article was to describe the essential concepts of the split-mouth design, its underlying assumptions, advantages, limitations, statistical considerations, and possible applications in Paediatric Dentistry clinical investigation.*

Discussion *In Paediatric Dentistry clinical investigation, and as part of randomised controlled trials, the split-mouth design is commonly used. The design is characterised by subdividing the child's dentition into halves (right and left), where two different treatment modalities are assigned to one side randomly, in order to allow further outcome evaluation. Each participant acts as their own control by making within-patient rather than between-patient comparisons, thus diminishing inter-subject variability and increasing study accuracy and power. However, the main problem with this design comprises the potential contamination of the treatment effect from one side to the other, or the "carry-across effect"; likewise, this design is not indicated when the oral disease to be treated is not symmetrically distributed (e.g. severity) in the mouth of children. Thus, in spite of its advantages, the split-mouth design can only be applied in a limited number of strictly selected cases.*

Conclusion *In order to obtain valid and reliable data from split mouth design studies, it is necessary to evaluate the risk of carry-across effect as well as to carefully analise and select adequate inclusion criteria, sample-size calculation and method of statistical analysis.*

Keywords *Clinical trials; Paediatric Dentistry; Split-mouth design; Treatment comparison.*

Introduction

Randomised controlled trials represent the optimal design in paediatric clinical investigation to compare performance and response between a novel restorative material or a therapeutic procedure (experimental) and another, already known, one employed as reference intervention or placebo (control). The treatment modalities are applied randomly to the oral cavity of two groups of children, where participants are followed during specific periods to measure outcomes-of-interest, in order to discern the real effects of the experimental treatment under investigation as opposed to those of the control [Brignardello-Petersen et al., 2015]. In some cases, limited resources for performing clinical trials and the difficulties regarding enrollment and maintenance of paediatric participants over the course of the study renders it critical for collecting high- quality information from each study [Antczak-Bouckoms et al., 1990]. Therefore, alternative clinical investigation methods have been developed.

One of these alternative methods is the Split-Mouth Trial (SMT). The design entails, in its simplest version, subdivision of the child's dentition into halves (right and left), where one of two different treatment modalities is assigned to one side randomly to allow comparison of outcomes after an appropriate follow-up period [Lesaffre et al., 2007]. There is another design in dental clinical investigation that is very similar to the SMT, known as the cross-over, which are sometimes erroneously considered synonyms [Antczak-Bouckoms et al., 1990; Lesaffre et al., 2009]. In cross-over designs, each patient randomly receives the two study treatments in two different sequences (A-B or B-A) at different times, with an intermediate period (known as the wash-out period) that allows the effects of the first treatment to disappear from the system prior to administering the second one (as observed when two distinct anti-caries mouthwashes in children are compared). On the other hand, in the SMT design, both treatments may be applied simultaneously in the same session without a wash-out period [Antczak-Bouckoms et al., 1990; Foley et al., 2004; Lesaffre et al., 2009; Pandis et al., 2013]. Thus, SMT is considered a type of cross-over design, where "time" is replaced by "site" in the mouth [Lesaffre et al., 2009].

The SMT is also indicated for other, more complex mouth subdivisions - e.g., quadrants or sextants, in multiple combinations (contralateral, diagonal, or ipsilateral) -, employed particularly in Periodontics, Orthodontics, and Cariology investigation [Morrow et al., 1992; Lasaffre et al., 2007; Pandis et al., 2013] and representing >11 different variants [Pandis et al., 2013]. The aim of this report was to describe the essential concepts of the SMT, its underlying assumptions, advantages, limitations, statistical considerations, and applications in Paediatric Dentistry clinical investigation.

The basics of the SMT

The SMT was first introduced in the late sixties by Ramfjord for application in periodontal clinical trials [Pandis et al., 2013]. It is considered a unique, self-controlled randomised trial in which the simplest version anatomically splits the oral cavity into left and right halves by means of the mid-sagittal plane between the central incisors [Lasaffre et al., 2009], with the aim of evaluating the effect of an experimental procedure on one side, and comparing it with its contralateral equal (Fig. 1). Experimental units can comprise an individual tooth or even a tooth surface [Antczak-Bouckoms et al., 1990]. Because innervation of orofacial structures depends on individual right/left trigeminal nerves, nociceptive responses can be measured and correlated with the treatment assigned. This important fact avoids the bias of how to standardise the painful response of the individual participants of a certain experimental group.

In Paediatric Dentistry, this design is especially useful to compare restorative materials or local preventive agents (e.g., fissure sealants or topical fluoride varnishes), in cases of diseases whose characteristics are symmetrically distributed throughout the patient's dentition (e.g., equal distribution of carious cavities in primary molars on both dentition sides) and when it is possible to record data from equivalent experimental and control sites in the mouth of the same individual, using participants as their own controls [Riordan and FitzGerald, 1994]. By performing within-patient rather than between-patient comparisons, the study's variability or random error can be significantly reduced, decreasing the majority of inter-subject variability in terms of the treatment effect, thus increasing study accuracy and power to detect real differences with fewer participants (different from the traditional, two-arm parallel trial) [Hujoel et al., 1990; Lasaffre et al., 2009]. By avoiding possible bias and the comparison of two groups,

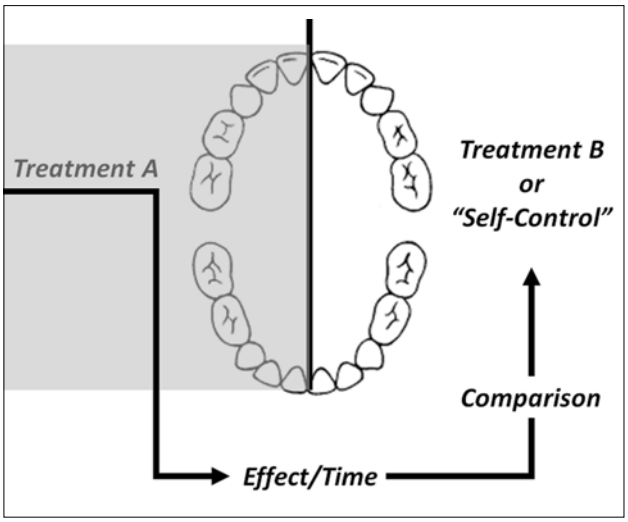

FIG. 1 Schematic diagram of a simple Split-Mouth Trial in Paediatric Dentistry (treatment vs. treatment).

SMT also diminish the number of subjects required.

However, important mishaps can take place when SMT is employed by oral health investigators, such as risk of "contamination". This event occurs when the treatment performed on one side of the mouth affects the treatment outcome on the other side, creating under- or overestimation of the effect observed. This bias is termed the carry-across (or carry-over) effect [Hujoel et al., 1998]. Because the carry-across (or independence between treatments) cannot be quantified by statistical tests, it should be subjectively estimated by the investigators, based on their own clinical experience or on *a priori* substantial knowledge on biological arguments and the characteristics of treatments or materials under investigation. If carry-across is considered null or negligible, then the use of the SMT is justified and the study results are more accurate. For example, for restorative materials of pulp treatments applied in Paediatric Dentistry, the occurrence of a carry-across effect from one material (or pulp treatment) to another appears very unlikely, in that the expected responses are solely attributed to each treatment. However, in cases in which two different systemic drugs are compared, two fluorides from toothpastes, or two mouthwashes, the risk of contamination bias is potentially high, because these interventions can provide their therapeutic actions in a widespread manner, or be introduced freely within the whole oral cavity. Thus, the SMT should be avoided and a parallel design is therefore recommended [Hujoel et al., 1998].

Another important aspect is that SMT offers homogeneity between study "groups" regarding individual variables, such as age, oral hygiene level, systemic health, or caries status, before the treatment is administered. This condition renders the trial's results more valid and reliable [Pandis et al., 2013]. On the other hand, the main disadvantages of SMT include the faulty recording of any variable and possible patient loss during the follow-up period, because each patient represents both the treatment and the control. When these aspects are significant, study outcomes may be invalidated [Antczak-Bouckoms et al., 1990].

In summary, there are three main indications for conducting an SMT in Paediatric Dentistry clinical investigation [Hujoel et al., 1992; Pandis et al., 2013] as follows: symmetrical distribution of the study disease (for instance, carious cavities) within the dentition (matching sites); no presence of any carry-across effects of the treatment, and when the carry-across effect is present (but negligible or of a small magnitude), a valuable accurate result can be expected.

Methodological considerations

As in the classical controlled trial, planning and conducting an SMT should contemplate diverse methodological and ethical assumptions. Considerations with respect to blinding, allocation, concealment, and bioethical principles

are in essence the same [Hujoel et al., 1998; Pandis et al., 2013]. However, randomisation, sample-size calculation, or statistical analysis of the results can be applied somewhat differently [Kiriakou et al., 2014]. These issues will be reviewed later.

Randomisation

Random allocation of mouth sides and treatments leads to a fair comparison between study groups and minimises the effect of a potential confounding bias (identifiable or unidentifiable) of the results [Hujoel et al., 1998; Lesaffre et al., 2007]. In an SMT design, there are two study treatments (A and B) that are randomly assigned to Left or Right dentition sites (L and R) [Zhu et al., 2015]. Within the randomisation methods available (simple, restricted, stratified, and minimisation), the block scheme is popular in SMT [Hujoel et al., 1998]. In this method, both the "site" (in the majority of cases, an individual tooth) and the "treatment" are randomly allocated, creating a pair of matched data (two outcome measures per each participant); thus, both study groups have an equal amount of data [Lesaffre et al., 2007; Pandis et al., 2013]. The traditional block randomisation process can be modified according to the investigator's needs, involving recruiting "sites" and "treatments" in short blocks and ensuring that one half of the "sites" within each block are allocated to "treatment A" and the remaining one half to "treatment B" within each block to obtain the different combinations. The order of "site/treatment" combinations is organized into six diverse schemes. The six blocks of size four representing the six possible ways that four "site/treatment" combinations can be split evenly, as depicted in Figure 2.

Sample size

One of the main advantages of using SMT designs is their efficacy in terms of sample size, in that the participants are their own controls; in consequence, much inter-subject variability is avoided from the estimated effect, in comparison with studies in which the patient receives only one of the interventions [Pandis et al., 2013; Zhu et al., 2015]. This allows the enrollment of fewer subjects than in a parallel-group trial, maintaining the same power and saving resources [Pandis et al., 2013]. According to Antczak-Bouckoms et al. [1990], SMT and cross-over designs require only one half the number of participants to produce the same accuracy as traditional, two-arm parallel clinical trials. In order to calculate an adequate sample size, Pandis [2012] and Zhu et al. [2015] developed a compilation of formulas to aid investigators in designing SMT in children. For instance, to perform a sample size calculation for 2 paired means (outcomes as continuous data) with a 1:1 allocation ratio (e.g., left lower first primary molar vs. right lower first primary molar), the applying formula in this case is:

$n = f(\alpha,\beta) \times [\sigma^2 / (\mu 1 - \mu 2)^2]$

where σ is the standard deviation of the within-subject differences ($\mu 1 - \mu 2$), and $f(\alpha,\beta)$ is a function of power and significance level of 5% ($\alpha = 0.05$; $\beta = 7.85$, with 80% power and 10.5 with 90% power).

For example, let us suppose that a paediatric dentistry researcher is comparing the physiological root resorption in millimeters (as outcome variable), between two lower first primary molars (left vs. right) treated with pulpotomy and two different radicular pulp-capping materials. Aided by a biostatistician, the researcher assumes a difference between the two means ($\mu 1 - \mu 2$) of 0.5 mm, with a standard deviation (σ) of such a difference of 0.7 mm, $\alpha = 0.05$, and power = 90%; then:

$n = 10.5 \times [0.7^2 / (0.5)^2] = 21$

Thus, the researcher needs 21 children (or 42 pulpotomies) for his/her clinical study. In this study the carry-over effect is considered null.

For binary or dichotomus outcomes, the calculations are more complicated since the sample size should be adjusted according to a correlation coefficient (Pearson's r) [Pandis, 2012]. This procedure is not within the scope of the present work, so we suggest the reader also consult to Jolious et al. [1999] and Donner et al. [2007].

Statistical analysis of the results

Statistical analysis of an SMT design is complex. An essential feature of a split-mouth is that paired outcomes within every participating child are correlated between each other, and this aspect should be considered when a test is selected [Riordan and FitzGerald, 1994; Hujoel et al., 1998]. In the basic version, outcomes or results are most commonly expressed as continuous (quantitative) or binary types (categorical with only two response type, e.g. "yes" or "not") [Antczak-Bouckoms et al., 1990; Tobi et al., 1998; Lesaffre et al., 2007; Pandis et al., 2013]. For continuous results, the paired Student t test or the non-parametric Wilcoxon signed-rank test is recommended, whether or not the data are normally distributed. For binary results (percentages from two categories), the McNemar chi-squared test and the relative risk calculation are those most frequently employed [Riordan and FitzGerald, 1994; Lesaffre et al., 2007; Lesaffre et al., 2009]. For more

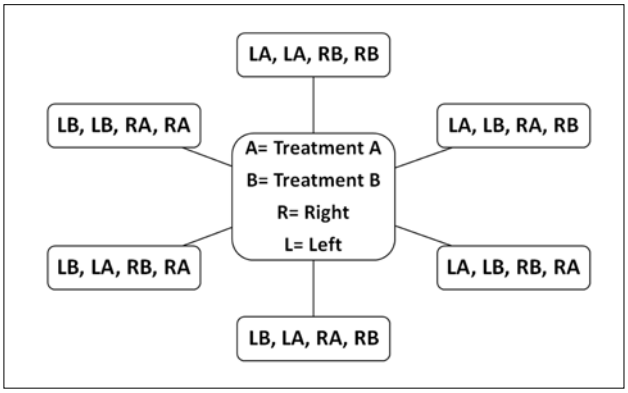

FIG. 2 Modified randomisation for Split-Mouth Trials in Paediatric Dentistry.

complicated designs (e.g., repeated measures, multiple comparisons for several teeth on the same dentition side, or >2 sites or treatments, caries trials, or survival outcomes), diverse methods that account for the correlated nature of data should be considered (e.g. regression models) [Rock, 1984; Riordan and FitzGerald, 1994; Hujoel et al., 1998; Tobui et al., 1998; Pandis et al., 2013].

Literature search strategy and results

An exhaustive web literature search of relevant references about the SMT in paediatric dentistry was conducted between January and February 2016, under the clinical research question: Are there examples of high-quality SMT articles in the paediatric dentistry literature? Two electronic databases were exhaustively explored (publication date since 2000 up to 2016), restricted to English language: MEDLINE (via PubMed) and EMBASE (Elsevier Science). The patient population included was subjects between 0 to 18 years of age, and the minimum sample size was determined in 30 participants. Search terms were: split-mouth design AND clinical investigation AND (pediatric dentistry OR pedodontics OR dentistry for children). Thus, the following search algorithm was developed:

(split-mouth[All Fields] AND design[All Fields]) AND ("Clin Investig (Lond)"[Journal] OR ("clinical"[All Fields] AND "investigation"[All Fields]) OR "clinical investigation"[All Fields]) AND (("paediatric dentistry"[All Fields] OR "pediatric dentistry"[MeSH Terms] OR ("pediatric"[All Fields] AND "dentistry"[All Fields]) OR "pediatric dentistry"[All Fields]) OR ("pediatric dentistry"[MeSH Terms] OR ("pediatric"[All Fields] AND "dentistry"[All Fields]) OR "pediatric dentistry"[All Fields] OR "pedodontics"[All Fields]) OR ("dental care for children"[MeSH Terms] OR ("dental"[All Fields] AND "care"[All Fields] AND "children"[All Fields]) OR "dental care for children"[All Fields] OR ("dentistry"[All Fields] AND "children"[All Fields]) OR "dentistry for children"[All Fields])).

The obtained list of detected titles and abstracts was reviewed in detail to select the appropriate articles. Selected articles were then obtained in full text. Additionally, a hand search was performed along the reference lists from each chosen full-text manuscript; to discard duplicity, a careful further exploration was done. Final included split-mouth articles were independently screened in a critical manner, to evaluate their methodological quality and/or internal validity (risk of any type bias, particularly the contamination bias). Any discrepancy was resolved by discussion among the three authors. Then, pertinent information for this review was extracted from these papers using a pre-designed form. As results, nineteen articles that meet the selection criteria could be retrieved in full text (Lo et al., 2001; Meechan et al., 2001; Hubel et al., 2003; Foley et al., 2004; Kavvadis et al., 2004; Palm et al., 2004; Sköld-Larsson et al., 2004; Lampa et al., 2004; Garrocho et al., 2009; Araposthatis et al., 2010; Maher et al., 2011; Arrow, 2012; Fallahinejad Ghajari et al., 2013; Chen et al., 2013; Aykut-Yetniker et a, 2014; Chavarría-Bolaños et al., 2014; Khorakian et al., 2014; Chavarría-Bolaños et al., 2015; Ünal et al., 2015). From these, four articles were selected as examples of well designed and conducted SMT studies (Table 1).

Study	Aim	Treatments	Randomization unit/ Method	Sample size	Statistical analysis	Conclusion
Lo et al., 2001	Clinical performance of two glass-ionomer cements for ART treatment, over 2 years	ChemFlex and Fji IX GP	Bilateral matched pair of primary carious molars with Class I or II cavities/Random table number	202 molars	Fisher's exact test Chi-square test Paired t test	The clinical performance of both cements for ART was similar over the 2 year period
Garrocho et al., 2009	Clinical and radiographic efficacy of two dressing materials for direct pulp capping, over 12 months	Calcium Hydroxide and Emdogain®	Two primary first or second primary molar per patient, distributed to contralateral halves/ Random numbers generated by a computer	90 molars	Fisher exact test	No significant difference between both direct pulp capping materials
Aykut-Yetniker et al., 2014	Interaction of two materials with caries affected dentin, and the remineralization levels, in ART treatments, during 2 years	High viscosity glass-ionomer cement and Composite resin	Contralateral carious primary molars/ Randomization method not described	24 molars	Repeated measure ANOVA and post-hoc Bonferroni test	GIC was a better restorative material for the remineralization of carious dentin. Dentin microhardness adjacent to the material was significantly higher
Khorakian et al., 2014	Clinical and radiographic success rate (over 24 months) of pulpotomies with two techniques	Calcium-enriched mixture and ZOE after electrosurgery	Contralateral first and second primary molars/Random numbers generated by a website	102 molars	McNemar test	The treatment success rate was similar in both pulpotomy techniques

TABLE 1 Examples of Split-Mouth Trials (SMT) in the Paediatric Dentistry.

Conclusion

Well-developed, randomised controlled trials and their variants offer the highest level of evidence concerning the effectiveness of new interventions. Under certain circumstances, SMT represent a more efficient tool in Paediatric Dentistry clinical investigation. However, special care must be taken when opting for this type of design, first considering all of its advantages and its potential. In addition to the bioethical standards that apply for minors and other vulnerable populations, it is strongly advisable to review other methodological issues prior to initiating SMT as follows.

- Proper eligibility criteria for participants, assessing the symmetrical distribution of the disease within the oral cavity.
- Careful evaluation of the risk of the carry-across effect between the study interventions. Remember that most preventive/restorative dental materials utilised in children have only a local effect; thus, the presence of carry-across effects is nearly null.
- An adequate sample-size calculation process.
- Selection of an appropriate statistical analysis of the data.

The evidence generated on developing SMT may be as valid and reliable as that from traditional, parallel clinical trials.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Compliance with ethical standards

None applied.

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