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UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO"
Instituto de Ciência e Tecnologia
Campus de São José dos Campos



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LITERATURE REVIEW

doi: 10.14295/bds.2017.v20i2.1404

Guidelines for conducting split-mouth clinical studies in restorative dentistry

Guia para condução de estudos em boca dividida em dentistica

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ABSTRACT

The split-mouth design used in some clinical trials make a randomization scheme on site level where two treatments are randomly assigned to sites of one of the two halves of the mouth. The aim of this review was to summarize guidelines for conducting split-mouth clinical studies in Restorative Dentistry. This is a review performed through scientific articles published between 2004 and 2014 indexed in MEDLINE, PubMed and Scielo databases. The study evaluated USPHS and FDI criteria. The current review showed the main characteristics used in split-mouth studies presented the Restorative Dentistry literature, as ethical aspects, sample calculation, methods of selection and evaluation patients, in order to provide a guideline for clinical conduction. It showed a standard of methodologies to enable comparison among studies.

KEYWORDS

Clinical studies; Split-mouth design; Dentistry.

RESUMO

O desenho experimental proposto em estudos clínicos do tipo boca dividida objetivam uma aleatorização em nível local, no qual dois tratamentos são randomizados em cada um dos lados da boca. O objetivo dessa revisão foi resumir em um guia as normas para condução de estudos clínicos do tipo boca dividida na área de Dentística Restauradora. Foram selecionados estudos clínicos indexados nas bases de dados MEDLINE, PubMed e Scielo, entre 2004 e 2014, que utilizaram o critério USPHS ou FDI. O presente guia mostrou as principais características que devem ser consideradas em estudos do tipo boca dividida na área de Dentística, tais como os aspectos éticos, calculo amostral, métodos de seleção e avaliação e pacientes, como forma de facilitar e conduzir estudos clínicos.

PALAVRAS-CHAVE

Estudos clínicos; Dentística; Boca dividida.

INTRODUCTION

Since World War II experiments with human beings have become more delicate, creating several rules and ethical aspects to the increasing employment of patients as experimental subjects [1]. Investigators are responsible for all subjects enrolled in a trial, not just some of them, and the goals of the research are always secondary to the well-being of the participants. Those requirements are made clear in the Declaration of Helsinki of the World Health Organization (WHO), which is widely regarded as providing the fundamental guiding principles of research involving human subjects [1].

Mainly, the clinical trials are randomized and controlled, in which the subjects of the research are distributed in the different treatment groups. Also, the clinical studies can be classified in crossover, when the same subject

is participant of the treatment and the control groups. In this last case, a washout period must be taken [2]. In Dentistry, when evaluating restorative treatment options, the split-mouth design in commonly used.

The split-mouth design used in some clinical trials make a randomization scheme on site level where two treatments are randomly assigned to sites of one of the two halves of the mouth [3]. The split-mouth design is a dental version of an agricultural split-plot design where the geographical plots are replaced by regions in the mouth [4]. In dental clinical trials, often the aim is to evaluate the effect of an experimental treatment on a site in the mouth, e.g. a tooth or a surface on a tooth, and therefore, this design seems useful.

The concept of this design was introduced in 1968 by Ramfjord et al. in a periodontology study comparing two types of periodontal therapy by randomizing the treatment methods to half of each subject's dentition divided by the mid-sagittal plane between the central incisor teeth [5]. Since this date, it has become increasingly popular in oral health research, once in a split-mouth design, divisions of the mouth (dental arches, quadrants, sextants or smaller subdivisions) constitute the experimental units randomly assigned to treatments. Because the patient serves as his/her own control, which can increase statistical efficiency, on average, fewer patients are needed [4], but on the other hand, this study design require that the patients present symmetric conditions in both sides of the mouth [3].

Thus, the aim of this review is to summarize guidelines for conducting split-mouth clinical studies in Restorative Dentistry.

MATERIAL AND METHODS

The recommendations assigned in this guideline were made upon review through scientific researches published between 2004 and 2014 indexed in MEDLINE, PubMed and Scielo databases. The search databases were performed using the USPHS and FDI criteria. The inclusion criteria were studies related to clinical trials and split-mouth in Dentistry. We excluded studies that addressed other factors that were not related to the descriptors above. Also, we excluded the use of abstracts, by not providing full analysis of the studies presented.

Guidelines for split mouth research in dentistry

The steps for conducting a clinical trial in restorative dentistry are: the definition of the study strategy (randomized controlled, crossover, split-mouth, etc), the sample size calculation, the patient selection, the time the study is conducted (short or long term evaluations), the evaluation criteria.

Clinical Studies Involving Humans

Clinical researches in Restorative Dentistry come in expansion over the last years to conduct clinical trials with new restorative materials and techniques available in the Brazilian and worldwide market.

Firstly, in clinical studies, it is necessary to approval of the study protocol by the Research Ethics Committee or by the National Commission Research Ethics [6]. The regulation of clinical research by the Ethics Committee provides assurance that the rights of human subjects involved in the research are respected.

Secondly, studies involving humans requires the consent of the research subject prior its participation in the study. The so-called term of consent must be signed, dated and documented in the study. This term protects individual freedom of choice, respects the autonomy of each individual, ensuring voluntary participation in the study [7].

Thus, clinical research involving human beings needs approval of Research Ethics Committee and the acceptance of subjects involved signed.

Split-Mouth Evaluations

The main purpose of the split-mouth design is to remove all components related to differences between subjects from the treatment comparisons, by making within-patient comparisons, rather than between-patient comparisons, [3,8]. While these designs offer potential savings in resources, their usefulness can be negated if several strict scientific and statistical assumptions are not met [9]. The requisites for the use of split-mouth designs are that: the disease to be investigated is relatively stable and uniformly distributed; the effects of the treatments to be evaluated are short lived or are localized for split-mouth designs [9].

Split-mouth clinical studies are characterized by division and assessment methodology covering at least two teeth or mouth areas. The patient receives the treatment on each side of the mouth, divided as quadrant or as sextant. In this type of study, the patient selection becomes more selective, since the patient should have the same standard of "disease" on both sides and areas assessed. This restriction might influence the selection of patients towards those with a higher risk for cavities and possibly poorer brushing and dietary behavior, for example [3].

Within the split-mouth studies, the clinical procedures are randomly performed by lottery through envelopes [10-13], by casting a coin [14-18] or computer programs that Randomize numbers; which allows each tooth or area of the oral cavity to receive one of the treatments, according to the experimental conditions.

From the randomized study, the procedures are performed by qualified and experienced professional. However, the operator has no access to data evaluated, i.e. the professional operator is different from the professional evaluator. The evaluator will have access to all responses (positive or negative) of the symptoms of patients and will not know the treatment that was selected, while the operator will not have access to patient information and only perform clinical procedures, characterized a double-blind study. Previous split-mouth studies, between 2014-2004, standardized 1to 3 professional operators [11,13-15,17-23] and 2 to 3 professional evaluators [11,13-21,23,24].

Sample Size Calculation in Split-Mouth Studies

The sample size is the number of participants planned to be included in the trial, usually determined using a statistical power calculation. In split mouth studies, usually the aim is to evaluate an intervention over a tooth or area, therefore each individual receives all modalities of intervention. Thus, the randomization must be performed within the studied areas and not within the patients [25]. The sample size should be adequate to provide a high probability of detecting as significant an effect size of a given magnitude if such an effect actually exists. The number of participants enrolled is the achieved sample size, treated or analyzed in the study [26].

The sample planning of a study determines the numerical dimension and also the sampling technique (collection/selection) of the elements of the study. It is essential in the elaboration of the project, and problems with such planning may com¬promise the final data analysis and interpretation of its results. A proper sample planning depends on basic knowledge of the study statistics and deep knowledge of the problem under investigation, in order to combine the statistical significance of the tests with the clinical meaning of the results [27-29].

The selection of a population fraction that makes up the study sample implies the investigator will assume a certain degree of error for the estimated values of population parameters to each variable; such sample error is quantifi¬able, and inversely proportional to the sample size [29,30].

When the population standard deviation or frequen¬cies of the variable are unknown, and the literature does not present any similar

data, a pre-test should be conducted with 30-40 subjects and the behavior of this subgroup should be considered as the population estimate [31].

In studies where several variables are important for the analysis of the studied outcome, i.e., are not only control or correction variables, it is necessary to calculate the sample size to each important variable of the study [32].

Longitudinal studies (prospective cohorts and clinical trials), as they require the patients' follow-up over long peri¬ods, can be affected by subjects who leave, quit, drop out, die or are excluded from the study. The initial sample calculation correction is recommended, increasing it at least 30%, in or¬der to overcome such sample losses. Drop-out subjects should be studied judiciously regarding their reasons for leaving and whether they present difference in the study variables in rela¬tion to the other study subjects, to identify factors specifi¬cally linked with the dropouts. When more than 30% of the subjects are lost to follow-up, the results of the whole sample may be compromised, regardless of the number of cases [32].

Whenever the sample size is very small (<30 measurements), the analysis of subgroups is more difficult and the performance of statistical trials is compromised. One should be, however, careful to prevent sample supersizing, which usually occurs when the access to large computer databases are available. Increasing the sample reduces the confidence intervals of estimates and allows the detection of differences between subgroups, which even if statistically significant, do not present clinical relevance [28,33-35].

There are some software applications in Portuguese, such as intuitive BioEstat [36], can offer free sample sizing modules or the software package nQuery Advisor [37] that offers simple efficient means of calculating power and sample size. The software Epi Info [38] also provides information on calculating sample sizes and can be obtained for little or no charge. However, sample sufficiency should be regarded as an important part of a study methodological planning, which has be integrated into the elaboration of hypothesis, study design, sampling techniques and data analysis and interpretation, for a successful investigation [32].

Patient Selection

According to previous split-mouth studies, the research subjects must be selected in accordance of the clinical objective for each study. As inclusion criteria, researchers must consider the good general health of the patients; adequate oral hygiene; absence of caries, pulpal injuries and periodontal disease; absence of parafunctional habits; presence of antagonist and proximal contact with adjacent tooth; do not make use of cigarettes, drugs or any medicament that might influence or interfere in the results; do not present abutments for fixed or removable prosthesis in the area of interest; in case of women, do not be pregnant; and have legal age to be participant in clinical studies [8-13,15,16,19,23,39-45]. The careful evaluation of these criteria is fundamental for the conduction of split mouth studies, and lack of correspondence in them make the patient suitable for exclusion in the study.

Time of Clinical Assessment

The assessment time is very variable and is deeply related to the treatment proposed, being commonly divided in short- and long-term evaluations. In restorative dentistry, short-term split-mouth evaluations usually aim to evaluate medicaments or treatments, such as for dentin hypersensitivity, for example. These studies can evaluate different treatments within weeks and a few months [39,46,47]. On the other hand, long-term studies usually aim to evaluate the longevity of materials and restorative procedures, such as adhesives, composites or indirect restorations; and tends to last for years [12,15,48-50].

Researcher should be aware of the necessity of patients follow up after the treatment, which

will also depend on the treatment and aim of the study. The first follow-up can be after 24 hours or even after one week; and the subsequent ones should occur in frequent intervals (each six month or annually) with the intent to verify the moment of failure.

Methods for Clinical Evaluation

Clinical trials require objective, reliable and relevant criteria to evaluate the performance of restorations [24,45]. The most common evaluation criteria in clinical trials are the USPHS (United States Public Health Services) and the FDI (World Dental Federation).

The USPHS criteria is a long-established method used in clinical trials, firstly published in 1971 by Cvar and Ryge, and reprinted in 2005 [42], and remains the most used system for evaluating important characteristics of dental restorations [24,44,51]. In the USPHS criteria the examiners gave scores for each criterion evaluated following a list of parameters described in Alfa, Bravo, Charlie and Delta. The Alfa parameter was designed to show satisfactory quality, whereas the Bravo was for and acceptable condition with slight deviations from ideal performance, and correction possible without damage to tooth or restoration; Charlie was for severe defects but prophylactic removal for prevention of severe failures (not have acceptable quality); and Delta was for failure with immediate replacement necessary [52,53]. Regarding restorations, for example, Alfa are restorations that have satisfactory quality and excellent clinical standard; Bravo are restorations satisfactory but not ideal (acceptable); Charlie are restorations that do not have acceptable quality and must be replaced by preventive reasons; and Delta are restorations with mobility, fractured or lost [24,42,52].

Among the years, the USPHS criteria suffered some modifications to fit different studies, involving more criterions such as retention, tooth vitality, marginal discoloration, marginal adaptation, postoperative sensitivity, caries occurrence, color match, cavosurface marginal discoloration, wear (loss of anatomical form or contour or loss of surface), presence of proximal contact, surface texture analysis. Table 1 characterizes this USPHS parameter often evaluated, according with the Alfa, Bravo, Charlie and Delta scores.

The evaluation methods usually applied during the USPHS criteria and modifications is visual inspection with an explorer: for retention, marginal integrity, wear, proximal contact (also the use of dental floss); thermal sensitivity test for tooth vitality; visual inspection with mirror for color match, cavosurface marginal discoloration and caries occurrence; blow of air for postoperative sensitivity [13,24].

In 2007, the FDI World Dental Federation developed new criteria for evaluating dental restorations, as an effort to organize the existent criterions [48,56-58] simultaneously published in three dental journals. The criteria were categorized into three groups: esthetic parameters (four criteria), functional parameters (six criteria), and biological parameters (six criteria). Each criterion can be expressed with five scores, three for acceptable and two for non-acceptable (one for reparable and one for replacement) [57,58]. However, few publications have used them until now. It is speculated that the FDI criteria is more sensitive for identifying difference in restorations than USPHS criteria, but more studies to confirm that is still needed [12,48,59].

According with the FDI criteria, the parameters are classified in: 1. clinically excellent/very good; 2. clinically good; 3. clinically sufficient/satisfactory; 4. clinically unsatisfactory (but reparable); and 5. clinically poor (replacement necessary). In the aesthetic parameter is evaluated the surface luster, the presence of attaining in the margin and in the surface, the color match and translucency and the esthetic anatomical form. In the Functional properties is evaluated the fracture of materials and retention, the marginal adaptation, the

Table 1 - UPHS parameter often evaluated, according with the Alfa, Bravo, Charlie and Delta scores

CRITERIA	SCORE
Retention	Alpha: restoration completely retained [13, 19, 22, 24, 48, 54]. Bravo: restoration partially retained [13, 19, 24, 48]. Charlie: restoration completely lost [13, 19, 24, 48, 54].
Tooth Vitality	Alpha: vital [13]. Bravo: non-vital with retracted pulp [13]. Charlie: non-vital, need for endodontic treatment [13]. Delta: non-vital due to restoration [13].
Marginal Discoloration	Alpha: there is no visual evidence of marginal discoloration. No difference between restorative material color and the adjacent structure color [13, 22]. Bravo: there is visual evidence of marginal discoloration between tooth structure and restoration, but the discoloration does not penetrate in the interface in a pulpal direction [13, 22]. Charlie: there is visual evidence of marginal discoloration between tooth structure and restoration, and the discoloration penetrates along the restoration in a pulpal direction [13, 22].
Marginal integrity	Alpha: The explorer does not stuck when it is passed from the restoration surface to the tooth or, if the explorer sticks, there is no visible fracture along restoration margin [13, 22, 24]. Bravo: the explorer sticks and there is no clear and visible fracture, where the explorer enters, indicating that the margin of the restoration is not adapted closely with the structure of the tooth. The dentine and/or base are not exposed and the restoration has no mobility [13, 22, 24]. Charlie: the explorer enters a mass defect of the fracture that extends to the dento-enamel junction [13, 22, 24]. Delta: the restoration is totally or partially fractured, mobile or missing [13, 22, 24].
Postoperative sensitivity	Alpha: no post-operative sensitivity [13, 19, 24, 48, 55]. Bravo: post-operative sensitivity is present [13, 19, 24, 55]. Charlie: Postoperative sensitivity with treatment need [55].
Caries occurrence	Alpha: there is no visual evidence of dark and deep discoloration adjacent to the restoration [13, 19, 22, 24, 48, 54, 55]. Charlie: there is visual evidence of dark and deep discoloration adjacent to the restoration, but it is not directly related to the cavosurface margin [13, 19, 24, 48, 54, 55].* *Some authors classify the presence of secondary caries as Bravo [22, 50]
Color match	Alpha: The restoration matches the adjacent tooth structure in color and translucency (shade) [19, 24, 54]. Bravo: Light mismatch in color, shade or translucency between the restoration and the adjacent tooth, but within the normal color range variations [19, 24, 54]. Charlie: The mismatch in color and translucency is outside the acceptable range of tooth color and translucency [19, 24, 54]. Delta: Esthetically displeasing color and translucency (shade) [19].
Cavosurface marginal discoloration	Alpha: No evident visual marginal discoloration, without difference between restorative material color and the tooth structure [14, 24, 48, 55]. Bravo: Evidence of marginal discoloration between tooth structure and restoration (removable, and usually localized) [14, 24, 48, 55]. Charlie: Evidence of marginal discoloration between tooth structure and restoration, and the discoloration penetrated along the restoration in pulp direction (deep staining and cannot be polished away) [14, 24, 48, 55].
Marginal adaptation or wear (loss of anatomical form or contour or loss of surface)	Alpha: The restoration shows continuity of existing or anatomical shape is slightly flattened. Probe does not catch [14, 19, 22, 24, 48, 54, 55]. Bravo: A concavity surface is evident and probe catches without gap. V-shaped defect in enamel only [14, 19, 22, 24, 48, 54, 55]. Charlie: Loss of restorative substance so that the concavity of the surface is evident and the base and/or dentine are exposed [14, 19, 22, 24, 48, 54, 55]. Delta: Restoration mobile, fractured or missing (not acceptable clinically) [14, 19, 22, 55].
Proximal contact	Alpha: Tight interproximal contact. It is difficult to pass the dental floss between the restoration and the adjacent tooth. Correct contour and healthy gums [19, 24]. Bravo: Smooth interproximal contact. It is relatively easy to pass the dental floss between the restoration and the adjacent tooth. The gingival tissue is healthy [24]. Charlie: Lack of interproximal contact. Food accumulate and gingival inflammation [19, 24].
Surface texture analysis (polishability)	Alpha: The surface has a smooth, glazed or glossy appearance, similar to enamel. There is no tactile perception of roughness [19, 22, 24, 54, 55]. Bravo: Slightly rough or dull when inspected with the explorer. There is no clear of pores or craters [19, 22, 24, 54, 55]. Charlie: Presence of pores or craters. When the tip of the explorer is passed on the pores or craters seen, it is trapped [19, 22, 24, 54, 55]. Delta: Rough and dull, not reflective [19].
Fracture	Alpha: no evident fracture [48]. Bravo: small chip, but clinically acceptable [48]. Charlie: failure due fracture [48].

wear and the proximal anatomical form (contact point and contour). At least, in the biological properties parameter is evaluated the postoperative sensitive and tooth vitality, the recurrence of caries, erosion and abfraction, the tooth integrity (enamel cracks, tooth fractures), the periodontal response, the adjacent mucosa and the oral and general health [57,58].

For examiners calibration, in 2008, a web-based training and calibration tool called e-calib (www.e-calib.info) was made available. Clinical investigators and other research workers can train and calibrate themselves interactively by assessing clinical cases of posterior restorations, which are presented as high quality pictures [57].

CONCLUSION

The current guideline showed the main characteristics used in split-mouth studies presented the Restorative Dentistry literature, as ethical aspects, sample calculation, methods of selection and evaluation patients, in order to provide a guideline for clinical conduction. It showed a standard of methodologies to enable comparison among studies.

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Date submitted: 2017 Mar 07

Accept submission: 2017 Apr 03