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Research Techniques Made Simple: Randomized controlled trials for topical drugs in dermatology: when and how should we use a within-person design?

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ABBREVIATIONS USED:

AE: adverse event

RCT: randomized controlled trial

ABSTRACT

Topical drugs are commonly used as first-line treatment for dermatological conditions. Depending on the disease and the drug, 3 main designs can be used for randomized controlled trials (RCTs) assessing topical drugs: the classical individual parallel design, the cluster randomized design, and designs allowing for within-individual comparisons, including the cross-over design (in which patients are randomized to a sequence of interventions) and the within-person design (also called the split-body design). Within-person design can be used to compare different drugs concomitantly in the same patient. Randomization does not concern patients but rather lesions or body sites within patients, and the drugs to be compared are applied to the different lesions/sites. This design considerably reduces inter-observation variability and thus the number of patients to be included in the trial (sample size). However, this design has major methodological constraints, especially the need to resolve the problem of a possible carry-across effect. We first describe the specificities of RCTs evaluating a topical drug. Second, we present the different designs available and discuss the methodological points that should be considered, especially for a within-person design. Finally, we compare the relevance of the within-person design to that of other trial designs by considering 3 different scenarios.

SUMMARY POINTS

- Trials of topical drugs require a detailed description of all application modalities, such as the amount of drug to apply, how to apply treatments, and the delay between drug application and use of hygiene products.
- Three main designs can be used when assessing topical drugs: 1) designs allowing for comparison between parallel groups, including the classical individual parallel randomized controlled trial (RCT), in which patients are randomized and one assessment is available per patient, and the individual parallel RCT with clustering, in which patients are randomized and allocated to one treatment, but several lesions from the patient are separately assessed; 2) the cluster design, in which clusters of patients are randomized and allocated to one treatment; and 3) designs allowing for a within-individual comparison RCT, including the cross-over design, in which individuals switch from one treatment to another after a wash-out period, and the within-person design, in which lesions are separately randomized and concomitantly treated and assessed.”
- In the within-person RCT, also called split-body RCT, left/right comparisons RCT or intra-individual comparison RCT, patients simultaneously receive topical experimental drugs and controls on different lesions or body sites, which reduces inter-observation variability.
- As compared with the individual parallel RCT design, the within-person design allows for reducing the number of patients to be included in the trial; thus the design is well adapted for rare diseases.
- The main constraint of the within-person design is the need to control the risk of the carry-across effect, that is, leakage of the treatment effect from one site to another for a patient simultaneously receiving different drugs on different lesions.
- The choice of design depends on the drug (systemic passage etc.) and the disease (number and extension of lesions, prevalence etc.).

INTRODUCTION

Skin diseases are common in the general population. Clinical presentations are highly heterogeneous depending on the disease, and management might involve surgery, physical therapy (lasers, phototherapy etc.), systemic drugs, topical drugs or devices.

Topical drugs are often used as first-line treatment. They are directly applied on the skin and have limited systemic effects in most cases. Currently, topical drugs represent a major cost to the public: for example, the US Medicare Part D expenditures for topical steroids between 2011 and 2015 were estimated at 2.3 billion USD (Song et al, 2017).

The most frequent classical design for trials is the individual parallel RCT design (Maruani et al, 2015). However, other designs are available (Figure 1). Because topical drugs can be applied to only one or several lesions, different drugs can be compared in a single patient at the same time: this design is called the within-person RCT. Contrary to the individual parallel RCT, the randomization units as well as the assessment units can be the patient or each lesion, as reported in trials of vitiligo (Whitton et al, 2015).

In this article, we describe and discuss the specificities of these within-person RCTs and offer guidance for when and how to use them.

SPECIFICITIES OF TRIALS OF TOPICAL DRUGS (Box 1)

As in trials of systemic drugs, trials assessing topical drugs require a detailed description of all characteristics of the intervention, including the drug dosage, frequency of application and duration of treatment but also the galenic formulation and drug components. In addition, concomitant topical drugs must be mentioned as well as cosmetics and hygiene care products, including the delay between drug applications and cleaning products, because they can interact. Another specificity is the difficulty in determining a standardized quantity of topical drug to apply (the number of fingertip units by cutaneous area in centimeters has

been used for example). The maximum quantity to be applied, the use of a glove or not, and the modalities of application should also be mentioned to be able to reproduce the protocol. Regarding controls, most trials use a topical inactive control even when it is not the most relevant (Wilkes et al, 2016). If an inactive control is chosen, the best one to use is the vehicle (i.e., the same components as the intervention except for the active product) and not an emollient, which can be slightly active for inflammatory skin diseases and would induce interpretation bias (Hon et al, 2013). Finally, topical drugs might have slight systemic effect if there is enough percutaneous absorption.

WHICH DESIGNS TO BE USED WHEN ASSESSING A TOPICAL DRUG

Skin conditions may present as a single lesion (a skin tumor, cutaneous malformation etc.), multiple countable well-limited lesions (vitiligo, chronic plaque psoriasis etc.) or multiple diffuse uncountable lesions (scabies, exanthema etc.). According to these presentations, several distinct designed trials can be considered (Figure 1 and 2):

1) The classic individual parallel RCT. Patients are randomized, and assessment involves the whole patient (Papp et al, 2016) or a single lesion on the patient.

2) The individual parallel group with clustering RCT. Patients are also randomized, but the treatment effect is assessed for each lesion treated with the topical drug. For example, the study by Cavalié *et al.* (2015), which evaluated 0.1% topical tacrolimus for vitiligo, included 35 randomized patients and 72 lesions assessed. Because each patient may have one or more lesions, the design is similar to a classical cluster RCT, in which patients are clusters, and vitiligo lesions are assessment units within clusters. These units are correlated, as in cluster RCT.

These 2 designs above lead to inter-individual comparisons, i.e. between parallel groups of patients.

3) The classical cluster RCT. Groups (clusters) of patients are randomized and allocated to one topical treatment. For example, Madan et al. performed a cluster RCT to evaluate the efficacy of a behavior change package including regular use of moisturizing cream to prevent hand dermatitis in nurses working in health care. In this trial, clusters were hospitals, and nurses, who corresponded to assessment units, were embedded within clusters. (Madan et al, 2019)

4)) The cross-over RCT. Patients are randomized to a sequence of interventions and switch from one topical treatment to another after a wash-out period. Therefore, patients act as their own control. This design is appropriate for chronic stable disease (e.g., recurrent aphthous stomatitis) in which topical treatments will have transient effects without carry-over effects between the 2 periods of treatment (Gorsky et al, 2007).

5) The within-person design. The lesions or body sites are randomized but the patient is not, and lesions or sites are further assessed. The patient concomitantly receives the topical intervention and the topical control. The within-person design is close to the cross-over design, but treatments are administered at the same time rather than consecutively. As for the cross-over design, the within-person RCT benefits from patients being compared to themselves. Thus, because each patient contributes to both groups and because it reduces inter-observation variability, the required sample size greatly decreases. This design has been used in studies of topical drugs for acne vulgaris: patients applied the experimental drug to the right or left side of the face and the control to the contralateral side, then each side was assessed. In such designs, assessment units within patients are correlated (Pandis et al, 2017).

METHODOLOGICAL ISSUES THAT MUST BE CONSIDERED WHEN PLANNING A WITHIN-PERSON RCT (Figure 3)

Eligibility criteria – for both patients and lesions

Eligibility criteria need to be specified for patients but also for lesions or body sites. For example, a trial on chronic plaque psoriasis requires eligibility criteria for the plaque also to avoid biased comparison. Also, if the dermatologic condition involves a single lesion (e.g., a wide patch of alopecia areata), the within-person design requires that the size of the lesion be large enough to be divided into 2 homogeneous areas and to include an area separating the 2 areas to limit inter-contamination of the topical drug applied. Similarly, baseline data must be collected for both patients and lesions or body sites.

Interventions – the carry-across effect

For a within-person RCT, the absence or negligible systemic passage of the topical experimental drug is required to avoid a carry-across effect. This effect can be defined as the potential leakage of the treatment effect from one site to another, by direct contact or systemic passage (Lesaffre et al, 2009) (Figure 4). Systemic passage of a drug depends on its molecular weight, its properties of retention in the dermis, its lateral diffusion by the dermal microvascular perfusion (blood and lymphatic vessels) and diffusion into tissue (Dancik et al, 2012), and the skin where the drug is applied (more systemic passage in case of wide area of application or severe alteration of the cutaneous barrier).

A carry-across effect would be associated with group contamination and therefore an underestimated difference in treatment effect estimates. This situation would be conservative for a superiority RCT but would also inappropriately favor a non-inferiority RCT. Methods to limit and detect the carry-across effect should be described in protocols. When a plasma dosage of the drug is feasible, blood samples for this dosage must be included in the protocol (Leducq et al, 2019).

Compliance – the use of a care provider optimizes the protocol

Simultaneously applying both treatments on the same patient may challenge compliance. Classically, medication electronic monitoring system caps, smartphone applications, motivational phone calls, weighting and questionnaires, despite several limitations (electronic caps do not guarantee that topical treatment is applied as an example), are used to enhance compliance (Svendsen et al, 2018). However, the very issue in a within-person RCT is contamination. Indeed, with evident superiority of one drug or in case of local side effects associated with a drug, patients might be tempted to apply the apparently “best” treatment to all lesions. The use of a care provider to apply the topical experimental drug and the control is expensive but allows for limiting this risk and optimizing compliance.

Outcomes and estimation

Within-person RCTs imply outcomes at the lesion level: global patient-reported outcomes such as quality of life cannot be used for drug comparison. Similarly, the evaluation of general adverse events (AEs) can no longer be related to one of the drugs applied. Therefore, local AEs are the most reliable (erythema, burning, pruritus).

Recruitment – patient must accept to receive both treatments

In within-person RCTs, each patient is assured of receiving the topical experimental drug and the control(s), which might be satisfying for patients reluctant to receive only a placebo as in individual parallel RCTs. However, all patients’ lesions do not receive the same topical drugs, which can lead to inhomogeneous aspects. A way to facilitate the patient’s agreement to be recruited is to provide the most effective topical drug for all lesions after the study has ended.

Blinding is more challenging

In within-person RCTs, the risk of unblinding can be increased because each patient receives both treatments, which allows for direct comparison of local effects. Therefore, as far as possible, objective outcomes are preferred, such as assessments of photographs or other systems.

Statistical methods

Statistical methods must take into account the correlation between the different lesions within a patient. With only 2 lesions/body sites per patient, paired tests should be used. If more than 2 lesions/body sites are included, linear or logistic mixed models should be used, as in a paired-matched cluster RCT. Otherwise, missing data must take into account this intra-patient correlation. In within-person RCTs, lost to follow-up and participant dropout will cause a loss of 2 observations but are expected to be balanced because each patient contributes to both the experimental and control groups.

WHEN TO USE A WITHIN-PERSON RCT

Here, we discuss the relevance of the within-person RCT by considering 3 different scenarios.

Scenario 1 – a RCT of a dermatologic condition that involves a single lesion (e.g., a wide patch of alopecia areata; Figure 5a)

In an individual parallel RCT for this condition, patients will be randomized and allocated to one treatment (topical experimental drug or control). The whole lesion will be treated with the allocated drug, and assessment consists of one outcome measure per patient. With the within-person RCT, the lesion will be split into 2 homogeneous areas: one area randomly allocated to

the topical experimental drug and the other to the control. Each area will be assessed, thus leading to 2 paired outcome measures per patient.

The individual parallel RCT is easier to conduct but requires a larger number of patients. The within-person RCT allows for reducing the number of patients, but also inter-observational variability in a pathology with significant disparity among patients. However, with the within-person RCT, the risk of the carry-across effect is high for this condition, especially by direct contact. One way to limit the effect is to define a large buffer zone between both areas, where no drug is applied, to avoid inter-area drug contamination. Finally, we must consider patients' acceptability of the within-person RCT regarding the potential hair regrowth over one half only of the patch of alopecia.

Scenario 2 – a RCT of a dermatologic condition involving several countable lesions (e.g., vitiligo; Figure 5b)

In an individual parallel RCT for this condition, patients are randomized, but 3 situations can be considered for outcome assessment: 1) all lesions receive the same topical treatment (experimental drug or control), each lesion is assessed, and a summary statistic is used, for only one global evaluation per patient (e.g., the Vitiligo Area Scoring Index); 2) one lesion or several lesions or all lesions receive the topical treatment, but assessment focuses on only one lesion (thus, one measure per patient is available), or; 3) all lesions receive the same topical treatment to which the patient was randomly allocated, but each lesion is separately assessed. Therefore, for one patient, there are as many assessment units as the number of lesions treated. This design is considered as an individual parallel RCT with clustering.

In contrast, we can use a within-person RCT, in which randomization is not at the patient level but at the lesion or body site level: lesions are randomly allocated to receive the experimental drug or the control, so the patient receives both treatments.

In this vitiligo scenario, the individual parallel RCT with clustering is an appealing design because it has the advantage to increase statistical power by using the maximum potential amount of data. The within-person RCT also has advantages because it allows for reducing the sample size and limiting inter-observation variability. However, it can be considered only if the carry-across effect is controlled: the treated lesions must not be too close to one another and the experimental drug must have negligible systemic passage (which should be controlled by blood sampling).

Scenario 3 – a RCT of a dermatologic condition involving multiple diffuse lesions (e.g., guttate psoriasis; Figure 5c)

In this scenario, patients (individual parallel RCT) or body sites that include a large number of guttate psoriasis lesions (within-person RCT) can be randomized. In the first case, the unit of randomization is the patient, and all lesions are treated in the same way; assessment is at the patient level by use of a global evaluation tool. If body sites are randomized, assessment is at the body site level, considering an overall evaluation of lesions at each site. Global assessment such as quality of life cannot be used for drug comparison because each patient receives both treatments. If we consider that quality of life is the most relevant outcome for guttate psoriasis, the individual parallel RCT would be preferred to the within-person RCT.

CONCLUSION

The choice of the most adequate design when planning a protocol, must take into account the type of disease (number of lesions), its prevalence, the relevant primary outcome, the risk for the carry-across effect, and patient's acceptability. There is no unique rule to follow, and discussions should optimally involve dermatologists, methodologists and patients.

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BOX

Box 1. Items to be specified for randomized controlled trials involving a topical drug

- ✓ Description of the characteristics of the topical drug
 - Dosage
 - Galenic formulation
 - Drug components
 - Frequency of application
 - Duration of treatment

- ✓ Definition of quantity of topical drug to apply
- ✓ Description of allowed concomitant topical drugs and cosmetics/hygiene care products
- ✓ Description of the delay between drug applications and cleaning products
- ✓ Description of potential systemic passage of the drug
- ✓ Description of the topical control and justification for the choice

TABLES

Table 1. Glossary

Term	Description
Carry-across effect	The potential leakage of the treatment effect from one site to another in a patient receiving 2 or more topical treatments.
Cluster RCT	Trials in which clusters of patients such as wards, practices, schools or villages are randomized rather than the patients themselves. They are usually used for evaluating health service organization and health policy, often with complex interventions targeted at the level of the cluster, the individual, or both. In the present paper, cluster RCTs correspond to trials in which patients with multiple lesions are randomized. Clusters are actually patients, and lesions are observational units embedded in patients.
Cross-over RCT	Patients are randomized to sequences of interventions and receive multiple interventions. Each patient receives each intervention in a separate period of time. There is usually a wash-out period between sequences. Each patient is his/her own control.
Individual parallel RCT	Patients are randomized to intervention A (experimental treatment) or intervention B (control treatment). The objective of a superiority individual parallel RCT is to show that intervention A is superior to intervention B. The objective of a non-inferiority individual RCTs is to show that intervention A is at least as good as intervention B in terms of efficacy.
Individual parallel RCT with clustering	Patients with one or several lesions are randomized, but the treatment effect is assessed for each lesion treated with the topical drug. Because each patient may have one or more lesions, the design is similar to a cluster RCT, in which patients are clusters, and cutaneous lesions are assessment units within clusters. These units are correlated, as in any cluster RCT.

Within-person RCT	Patients receive 2 or more treatments to different body sites. The unit of randomization is not the patient but an organ or a lesion (cutaneous lesions, eye, teeth etc.) or body area (arms, legs etc.). The within-person design is also called the split-body design or intra-individual comparison design.
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RCT: randomized controlled trial

FIGURE LEGENDS

Figure 1. Available designs for randomized controlled trials (RCTs)

Figure 2. Types of designs for trials assessing topical drugs according to the number of skin lesions

Figure 3. Advantages and limitations of the within-person randomized controlled trial design

Figure 4. Two ways to induce a carry-across effect: 1) direct contact between the 2 topical drugs; 2) systemic passage of the experimental topical treatment

Figure 5. Skin conditions used for scenarios: (a) alopecia areata; (b) patches of vitiligo; (c) guttate psoriasis