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Use of Excess Abdominal Tissue for Large Tissue Sampling: A Randomized, Controlled, Triple Blinded, Sample-Paired Clinical Trial

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Abstract

Background: Randomized Controlled Trials (RCTs) provide the highest level of clinical research evidence. The RCT-design is crucial for the data integrity and applicability of the trial results and trial designs are being introduced to optimize the data output and clinical integrity of RCTs. Here, we conducted a paired trial design for investigating the feasibility of multiple interventions by several applications.

Method: This article presents a randomized, controlled, triple-blinded, paired, explorative clinical trial. The trial not only pairs a control with a single intervention but also allows for testing multiple treatments simultaneously. The concept of this trial relies on utilizing abdominal skin in participants eligible for cosmetic abdominoplasty. The excess tissue serves as canvas for multiple treatments, and patients act as their own controls. Using this trial design, we were able to investigate three treatments injected into the subcutaneous tissue and eight treatments injected into the dermis.

Results: The trial was proven feasible in its design and allows investigation of multiple interventions and indications simultaneously.

Conclusion: In conclusion, we have successfully conducted a paired trial design and tested its feasibility. We believe that by using this trial design, many challenges in clinical fields such as wound treatment, dermatology, and plastic surgery can be circumvented, leading to better and more efficient translation from animal models to human clinical studies.

Keywords: Paired trial; Local applications; Biocompatibility; Topical application; Surgical interventions

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Abbreviations

CT: Computed Tomography; GCP: Good Clinical Practice; MSC(AT): Adipose-derived Mesenchymal Stem/Stromal Cells; RCT: Randomized Controlled Trial

Background

Randomized Controlled Trials (RCTs) are considered to provide the highest level of evidence and are the gold standard for the assessment of safety, efficacy, pharmacokinetics and pharmacodynamics in clinical research and drug development [1,2]. RCTs are commonly designed as simple two-arm trial approaches. To overcome some of the limitations of conventional two-armed RCT designs, a paired trial design can be explored [3]. This is most frequently done either by matching participants based on their demographics or by implementing crossover studies where treatments are given consecutively [4,5]. Paired trial designs will generate greater statistical power, thus reducing the number of patients included and the subsequent costs associated [3,6]. However, designing a paired RCT is challenging, which is why researchers often deselect these trial designs.

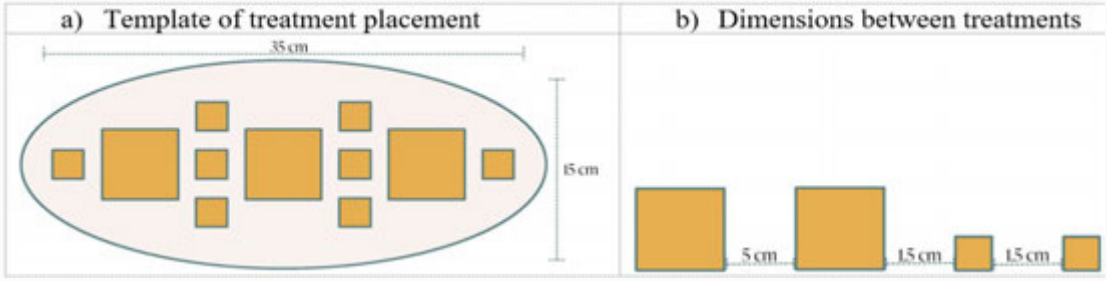

Figure 1: Template and dimensions.

In this paper, we introduce a RCT design to investigate several treatments and treatment indications in each trial participant, where each participant serves as their own control. Furthermore, we demonstrate that by applying this trial design, many of the challenges seen in surgical clinical trials such as biopsy limitations, unwanted surgical scars, unknown clinical outcomes leading to correctional surgery, and patient variance between active and control are eliminated [7-9]. In human studies, the lack of a sufficient number of tissue samples can create a gap of knowledge in the translation from animal studies, thus distort the perception of the investigated treatment [10]. This study design allows collection of numerous tissue samples, improving the quality of the study outcomes.

Furthermore, the RCT design is highly attractive for the participants as they all receive a desired abdominoplasty at the end of the trial period. Thus, the triallist, the investigator and the participants all benefit from this design.

The feasibility of the trial design is exemplified here by conduction of three potential treatment applications of adipose-derived Mesenchymal Stem/Stromal Cells (MSC(AT)), fat, and collagen for i) soft tissue augmentation ii) skin rejuvenation and iii) wound healing. The efficacy of the treatments will not be covered in this paper.

Method

Trial design

This is a randomized, controlled, triple blinded (surgeon, patient, and data assessor), paired, explorative clinical trial design approved by the Danish Committee on Biomedical Research Ethics: H-21004160, The Danish Data Protection Agency, The Danish Patient Safety Authority, and registered at ClinicalTrials.gov: NCT05079243. All participants signed a consent to participate form prior to enrolment. The trial was conducted at Aleris Hospitals, Søborg, Denmark. The essence of the trial design revolves around participants with an excess amount of abdominal tissue who are eligible for cosmetic abdominoplasty (the removal of excess abdominal skin and underlying tissue). The concept of this trial relies on utilizing abdominal subcutaneous tissue and skin already destined for resection. The sample size was determined to include 5 participants (expected mean of the paired difference =40, expected standard deviation of the paired difference =20, with 80% power and a level of significance of 5%). The sample size was determined from the lowest expected difference of the investigated applications. In this trial design it is important to correct for mass significance to avoid false significance's when testing multiple null hypotheses.

Due to the large dimensions of the abdominal skin to be resected, it was hypothesized that the skin and underlying soft tissue itself could serve as a major area for multiple treatments in the epidermal/dermal and subcutaneous layers.

The feasibility of testing multiple treatments in each participant was tested *in vitro*, prior to the trial, by drawing and measuring the size of the tissue before patients underwent conventional abdominoplasties in a plastic surgical outpatient clinic. After evaluation of the gross resection dimensions, we investigated the required dimensions of our injectable treatments by injecting dyed gel into the subcutaneous tissue and skin of already resected abdominal tissue. For skin injections, a treatment area of 2 cm × 2 cm was found sufficient to keep and hold 1 ml and ensure later sampling with certainty of sampling within the treated area. For the subcutaneous injections, an area of 5 cm × 5 cm of the resected abdominal tissue was deemed sufficient for sampling. A template was made in plastic to replicate the pattern on each trial participant (Figure 1).

The template comprised eight two by two-centimeter squares and three five by five-centimeter squares (Figure 2a). The pattern was fine-lined with permanent tattoos equal to that of the template to locate the treatments at the time of tissue sampling and at the end of the trial period (Figure 2b). The smaller squares were destined for dermal injections, and the larger squares were destined for subcutaneous injections.

The location of the different treatments was randomized using www.randomizer.org. A separate randomization sequence was performed for the subcutaneous and skin injections. The randomization sequences were printed and kept in a locked file cabinet until after data had been collected.

Documentation of treatments was performed in accordance with local regulations, ICH GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki. The participants were not financially compensated; however, they received abdominoplasty and body sculpturing without charge at the end of the trial.

The trial design related steps are shown in (Figure 3).

The CT scans were performed with a low radiation dose of less than 1 millisievert. The act of tattooing patients permanently was approved as the complete tattooed area was removed 180 days later during the abdominoplasty procedure.

Feasibility outcomes

Method for subcutaneous delivery: For the subcutaneous injections, the tattoos also made it easy to locate the area to inject and aided visibility on CT scans as small nada needles were placed in the lining of the squares during the CT scans. The steps involved in the subcutaneous injections are shown in Figure 4.

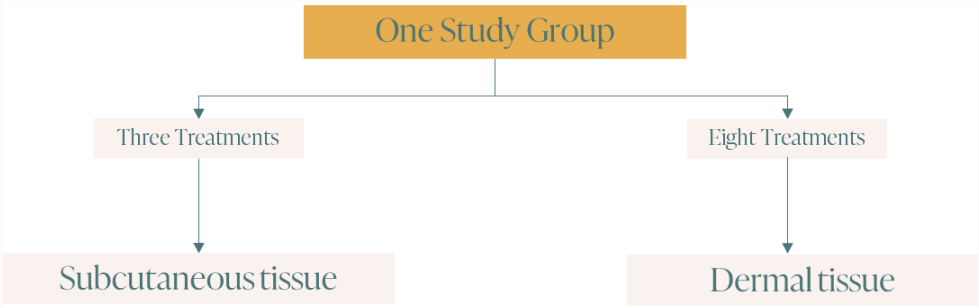

Figure 2: 2a Treatment numbers and locations.

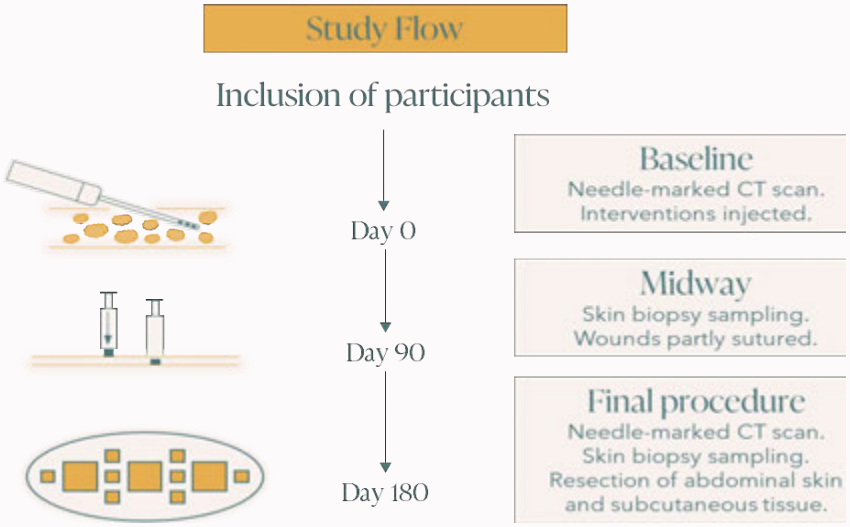

Figure 2: 2b Trial flow.

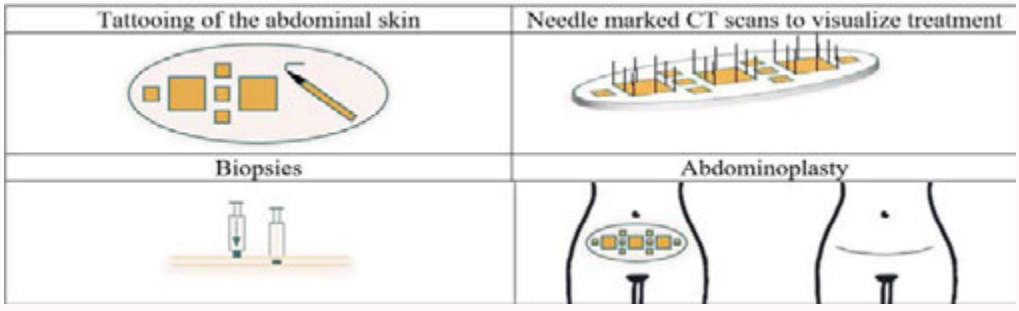

Figure 3: The trial design-related steps are as follows

Method for dermal delivery: For the dermal injections, the tattoos made it easy to locate the area to inject. After 90 days, 6 mm biopsies were taken from the eight treated areas to obtain tissue samples for determining changes in tissue composition and structure (Figure 5).

Wounds were inflicted 90 days after treatment when biopsies were taken, and the wounded area was excised 90 days later to assess wound healing.

Results

The trial design proved feasible in its flow, sampling from large tissue and removal of the area in an abdominoplasty. Volume changes using CT scans were not feasible to detect changes in grafted volume. The trial did not result in any adverse side effects.

Discussion

This RCT design proved feasible with some limitations. One concern was the rather comprehensive commitment by the trial participants. However, none of them expressed concerns regarding the steps of the study. It should be noted that even though the patients did not carry concerns it is from a clinical stand a substantial number of surgeries to undergo as part of a trial. The patients described an expected discomfort with the local anesthesia at the day 90 biopsies. Our research team expected some pushback from potential participants regarding the tattoos and nada needles at the time of CT scanning, but surprisingly, this step was not considered an issue by

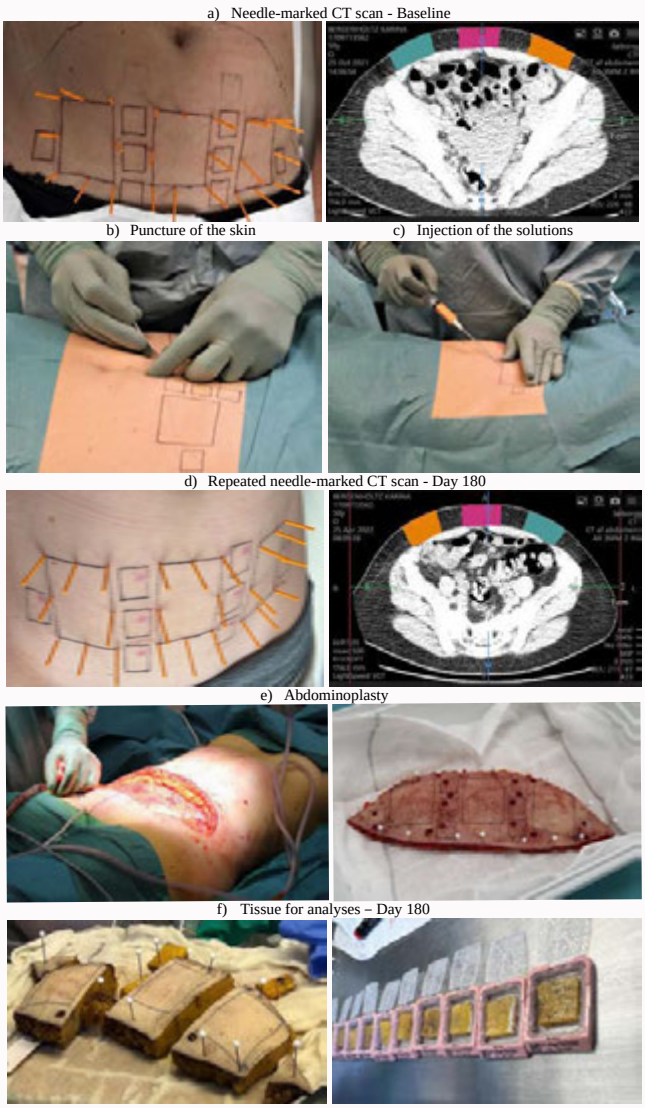

Figure 4: Subcutaneous application.

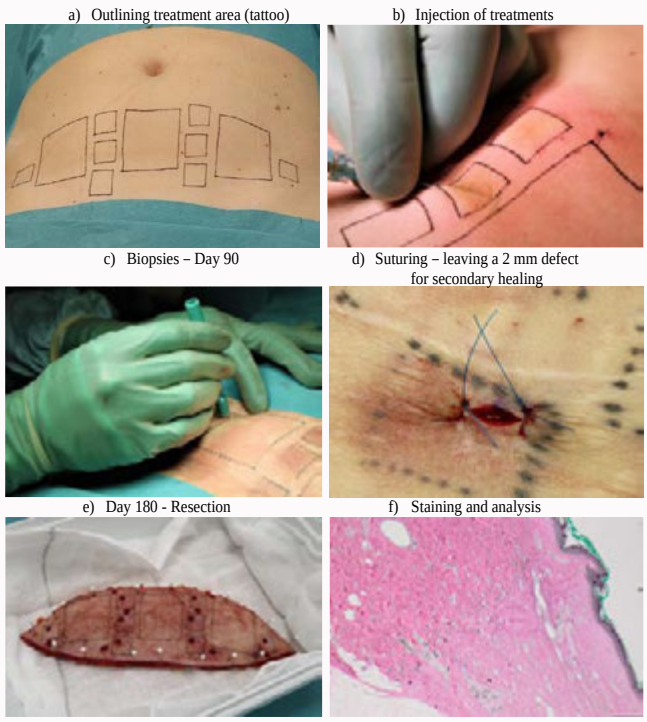

Figure 5: Dermal application.

the participants. Four out of five participants explained that they did not show their abdomen to anyone in private or in public, so they did not care weather a tattooed pattern was permanently left for six months. The compensation for participating was evaluated to provide a high driving force for recruitment and we had an overwhelming interest in the trial. It must be addressed that the compensation could potentially recruit participants blinded by the "end goal". Careful selection and thorough information are therefore necessary. The trial design made it possible to obtain large tissue samples both from the skin and subcutaneous tissue, which was the aim of the trial. One must however consider the possible systemic effect, but also the distance between areas, if there could be effects on areas in the proximity of the investigated intervention before injection or implantation. Interventions that provide systemic effects may not be suitable for this trial design. This must be considered for all paired designs, but as the trial allows for treatments to be placed side by side, the local effect of treatments must also be considered. The design involved an additional large surgery, although the procedure is a common plastic surgical procedure, it comes with added procedure-related risks for the participants.

After conducting this trial, we believe it holds potential for improving translation from animal to humans especially within the development of injectable or implantable treatments such as skin treatments, filler materials, meshes or other treatments not expected to induce a systemic effect. We also believe this design will benefit the investigator by providing abundant tissue for sampling while minimizing the number of required participants to generate sufficient power. If local toxicology is a concern, this could serve as a design to compare local tissue toxicology with sample materials and ensure the safety of tissue resection if the toxicology exceeds the expectations from preclinical trials. The design can serve as a canvas for testing desired drugs/devices with respect to participant discomfort and ethical considerations. As the total body of treatments is removed as the final part of the trial, one can argue that potential uncertainty, discomfort, and potential long-term side effects are reduced for the participants enrolled in the trial. Another potential application of the trial design is for dose–response studies. Investigators will attempt to find the perfect dose with the lowest side effects but are often limited in the possibility of testing different solutions *in vivo* [11]. This trial design could also allow for the testing of multiple established drugs/devices simultaneously or even to compare existing treatments. We believe that the trial design can be used for future development of wound dressings, suture materials, burn treatments, fillers, meshes and dermatological interventions.

The drawbacks of this trial design include i) the required access to surgeons who are able and willing to participate and ii) the relatively high cost to the surgeon if complete or partial compensation is ruled necessary by the investigator or local ethical authorities. However, the cost of abdominoplasty must be weighed against the cost of additional enrolment of participants. The additional steps for participants who would otherwise undergo an abdominoplasty can be designed according to the investigated drug/device. To the best of our knowledge, a design such as this that allows for extensive sampling of

tissue has not been previously described.

Conclusion

In conclusion, we have conducted a paired trial design, tested it, and demonstrated its feasibility. We believe that this trial design must be considered as an alternative to other more conventional trial designs, allowing for a better understanding of tissue alterations in response to the drug/device investigated and the mechanisms leading to efficacy and safety in humans.

Acknowledgement

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