Research Article

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Double-Skin: A New Approach in Laser Surgery Using the Regenerative Solution in Children Diagnosed with Vascular Anomaly: A Randomised, Double-blind, Placebo-controlled Trial

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Keywords: Laser Treatment; Vascular Malformation; Capillary Malformation; Venous Malformation; Sturge-Weber Syndrome

Abbreviations: LT: Laser Treatment; CM: Capillary Malformation; SWS: Sturge-Weber Syndrome; VM: Venous Malformation; Tas: Telangiectasias

ABSTRACT

Background: Laser treatment (LT) is the first-line treatment for Vascular Anomalies and allied syndromes, however it is associated with causes of the first-degree burns. Data on appropriate postoperative management is poor. Objective of the study was to examine the effect of the regenerative solution, compared with standard guideline-based management to improve future treatment options.

Methods: This is parallel-group, double-blind, placebo-controlled trial of children (aged 6-18 years) with clinically diagnosed Vascular Anomaly admitted to the Vascular Anomalies Centre between January 1, 2020, and August 27, 2021, in Moscow, Russia. After approaching 325 potentially eligible patients, recruited between January 1, 2020, and August 27, 2021, 200 patients were randomly assigned (1:1) either to a new approach in laser treatment (group A) or to the standard one (group B). This trial was registered with ClinicalTrials.gov, NCT 04999618

Findings: In early postoperative period, significant differences in clinical signs and symptoms were obtained. The median recovery time was increased in the group B with available data (7 days [IQR 0–9]) than in the group A with available data who received the regenerative solution (3 days [IQR 0–8]; p<0·0001; median difference 4 days [95% CI 1–3]). As for scale on the life impact of childhood skin conditions there was a statistically significant difference between groups A and B at 1-week (mean difference, 1.75; 95% CI 1–3; p=0.001), however there were no between-group differences at 3-week (mean difference, 0.65; 95% CI -0.20 to 1.50; p=0.134).

Interpretation: A new approach in laser surgery of Vascular Anomaly significantly reduces the duration of postoperative enhanced recovery. This data suggests that using the Regenerative Solution may lead to enhanced recovery by preventing negative outcomes of postoperative infection, and the likelihood of life-quality decrease in children.

Introduction

Laser Treatment (LT) is the first-line treatment for the most of Vascular Anomalies and allied syndromes. Over the past two decades, the adverse effect rates have been decreasing over the past two decades, reaching the low rate of 0.8% per treated patients per year. Significant advances have been made in recent years in the technological development of vascular lasers that can target cutaneous vascular disorders by selective photo thermolysis, so as most patients tolerate the procedures with minimal, if any, discomfort. Still pediatric patients commonly require conscious sedation or general anesthesia, especially when the large lesions are being treated. Surface cooling enhances efficacy and safety in skin laser surgery, however, even if an adequate cooling is employed, lesions which require higher fluences, may result in the epidermal damage. These may be pain, redness, vesiculation, and crusting. The longer pulse durations and a wavelength, which is also absorbed by melanin, has a higher incidence of side effects due to epidermal injury, likely related to excessive epidermal temperatures. However, the postoperative care commonly consists only of application of a healing ointment, and avoidance of sun exposure, to reduce the risk of post inflammatory hyperpigmentation [1-4].

During the first two weeks, erythema and edema are significant, and social activities come to a halt. Postoperative edema decreases after the first 4-5 days, whereas the erythema is prominent for the first week until re-epithelialization occurs and slowly diminishes over the next few weeks. The risk of infection, pigmentary changes and scarring is higher in the immediate postoperative period, as it is in any procedure where de-epithelialization occurs. We hypothesized that a new approach in the laser surgery, using the 1% aqueous solution of the partial silver polyacrylate Haemoblock, might be associated with reducing the time to clinical improvement. Haemoblock is known for both bactericidal and bacteriostatic effects, and which is likely decreases the risk of infection postoperatively [5]. Furthermore, it initiates the cascade of signals required for the tissue regeneration processes by plasmolyzing the polyacrylate matrix. In this study, we aimed to assess the clinical effectiveness of the regenerative solution Haemoblock in enhanced postoperative recovery in children undergone laser surgery relative to placebo [6].

Research in Context

Evidence before this study: We searched PubMed and the ClinicalTrials.gov on December 12, 2019, to find prospective studies in English, investigating the clinical effect of Haemoblock in the postoperative care. We used the search terms "Haemoblock", "Vascular Anomalies", "postoperative care", "postoperative management" "laser treatment" AND/OR "laser surgery". We did not identify any studies assessing the impact of applying this solution in pediatric patients with Vascular Anomalies in the postoperative care. We only have found studies, which generally proved the antimicrobial activity of the silver hydrogel dressings (Boonkaew et al. 2013). However, we identified one RCT standing that the Haemoblock might be associated with reducing the duration of the postoperative wound draining and the severity of pain and the need for analgesics. Therefore, we hypothesised that a new approach in laser surgery, using the 1% aqueous solution of the partial silver polyacrylate might be associated with reducing the time to clinical improvement [7].

Added Value of this Study: To our knowledge, this is the first prospective randomised controlled trial to investigate the effect of applying the regenerative solution postoperatively in children with Vascular Anomalies undergone laser surgery. We found that it leads to enhanced recovery.

Implications of all the Available Evidence: Our findings highlight that as postoperative quality of recovery is considered as a crucial outcome following surgery and anesthesia, more research is needed to further research understand the long-term impact of the use of Haemoblock as the regenerative solution.

Methods

Study Design and Patients

This parallel-group, double-blind, placebo-controlled trial was undertaken at the Vascular Anomalies Center (VAC) "Haemangioma" in Moscow, Russia. The study was approved by the local Ethics Committee was performed consistent with the ethical standards of the Declaration of Helsinki. Patients (≤18 years old) with confirmed Vascular Anomaly were eligible for inclusion in the trial if they met the criteria. Inclusion criteria were as follows: healthy males or females, Fitzpatrick skin types I–VI, aged ≤18 years old with clinically evident Vascular Anomaly. If so, the written informed consent was obtained. Exclusion criteria were as follows: keloid scarring, open wounds or atopic dermatitis in the treatment areas; any surgical, chemical or light-based treatments within the previous 6 months [8].

Randomization and Masking

Patients who fulfilled the randomization criteria and consented were randomly assigned (1:1) to receive either placebo or Haemoblock, together with laser treatment as usual. Randomization was done through a centralized, web-based system using a computer-generated minimisation algorithm. Administrator randomly assigned participants after verifying eligibility and obtaining patient consent. The trial was double blind, with solution and placebo identical appearance. In RCTs, randomization determines treatment allocation, which prevents selection bias

from distorting the measure of treatment effects, that's why participants, clinicians, and the research team, completing baseline and follow-up assessments were masked to group allocation [9].

Procedures

Before the surgery, a preoperative assessment (meaning gathering basic health related information such as medical history, pre-existing conditions, and current medication) was done. On the day of surgery, after all eligible documents and consents had been verified, patients were randomly assigned to either group A (intervention arm) or group B (control arm). All surgeries were performed under the general anesthesia. Pediatric metal corneal shields were used if the peri-orbital area was involved, otherwise latex-free hypoallergenic eye protection pads were used. As all procedures were done in day care, the patients were discharged within 3-4 hours after the surgery [10]. Then, patients were followed up at 7-days and 30-days, after the laser treatment. Patients who were not able to attend face-to-face follow-up appointments were contacted by telephone. The research team members attempted to contact patients three times before declaring them lost to follow up. If available by telephone, the patients were asked to provide their verbal consent to the interview. Outcomes at each stage were assessed by a pediatrician who did not do interventional procedures. Every 3 to 6 weeks, an independent trial steering committee and an independent data monitoring and ethics committee reviewed the trial to assess its conduct, progress, and safety.

Outcomes

The relationship between the severity of eczema and the negative impact on child's life-quality had been established a long ago. Despite the limitation of these studies, our hypothesis was that these symptoms might affect children and families' quality of life after the laser-treatment too. Thus the primary outcome was to evaluate the effect of the therapy on the time to clinical improvement, and secondary outcomes included the determination whether the using the regenerative solution has a beneficial effect on clinical progression of the disease and to assess its impact on the life-quality in children with skin conditions. Safety data were collected for all patients at each trial visit regarding adverse events if any, with seriousness defined as per Good Clinical Practice guidelines. More information on outcome assessments is available in the protocol.

Statistical Analysis

Descriptive statistics were calculated for baseline characteristics. Continuous variables were summarized as median (with interquartile range) and categorical variables as frequency (percentage). We used Microsoft Excel (Microsoft Corp, Redmond, WA, USA) for data collection, storage and management. The statistical analysis was approved by the trial statisticians and steering committee before data analysis. All tests was done two-sided. Owing to the descriptive nature of the study, there is no bias adjustment because of the adaptive design. All analyses were done in SAS (version 9.4). This trial is registered with ClinicalTrials.gov.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We recruited patients between January 1, 2020, and August 27, 2021, and completed follow-up interviews by October 2021. Overall, 325 participants were assessed for eligibility; after 125 participants were excluded, we randomly allocated 200 patients to the two groups, so that we had 100 patients in the group A and 100 patients in the group B (**Figure S1**). 91 participants of the group A and 93 participants of the placebo group (present at the 3-week follow-up) were included in the primary analyses (**Table S1**). By week 3, we made a sensitivity analysis and similar numbers remained in both groups. The median recovery time was increased in the group B with available data (7 days [IQR 0–9]) than in the group A with available data who received the regenerative solution (3 days [IQR 0–8]; p<0·0001; median difference 4 days [95% CI 1–3]). As for scale on the life impact of childhood skin conditions there was a statistically significant difference between groups A and B at 1-week (mean difference, 1.75; 95% CI 1–3; p=0.001), however there were no between-group differences at 3-week (mean difference, 0.65; 95% CI -0.20 to 1.50; p=0.134) (**Table S2**) (**Supplementary Text**).

Discussion

While we feel that the current study results are enough for adjusting a regenerative solution to become the preferred standard of care, more studies are needed. Future pharmacological and pharmaco-clinical studies are needed to evaluate the effect on the skin microbiome, and also to explain the healing-effect by standing which cytokines are involved and whether it has any influence on keratocyte differentiation improvement. Moreover, just as aftercare is an important component of achieving successful results, caring for the skin after the laser treatment is vital. Thus, we believe that further studies must assess if there is any beneficial solution to apply late postoperative period in addition to the aftercare. However, given the relatively low rates of toxicity reported in our study, these studies would require significant sample sizes. Concerning the progression of the study, the recruitment of patients was slower than had been originally planned. This could be partly attributed to the epidemiological situation due to the COVID-19 pandemic.

Contributors

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Interest

We declare no competing interests.

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Conflict of Interest Disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have nothing to disclose.

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