aesthetic medicine

Research

Preliminary clinical validation of cryoadipolysis treatment under effects of ischemia simulated by COMSOL Multiphysics® software

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Running head: Ischemia in cryoadipolysis

Abstract

Cryoadipolysis is a non-invasive technique for subcutaneous fat reduction, which is used to circumvent problems associated with surgical methods like liposuction or abdominoplasty. During cryoadipolysis, local ischemia is caused due to the suction process and blood flow is reduced. This leads to a reduction of the biological heat within the suctioned tissue, which can increase the cooling capacity of cryoadipolysis applicators. In this study we performed a preliminary clinical investigation to validate a mathematical model designed to determine the percentage of bloodstream that flows through treated tissue, depending on the geometric characteristics of the cryoadipolysis applicators used. We observed a very strong correlation (R2 > 97%) between experimental and simulation data. The use of numerical simulations and accurate models that reproduce the thermal behavior of biological tissues can be used to better understand the cryoadipolysis process, estimate the efficacy and safety of cryoadipolysis applicators, and develop better and safer devices.

Keywords

Ischemia, Cryoadipolysis, Simulation, Clinical study, Cooltech Define, COMSOL

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Introduction

Fat accumulation is a serious aesthetic and health concern for modern society.
Cryoadipolysis is a non-invasive technique for fat reduction that is used as an alternative technique to circumvent general problems associated with analogous surgical methods (i.e. liposuction)[1].
During cryoadipolysis, adipocytes are selectively lysed after local cold induction and no harm is caused to adjacent cells[1]. Since the approval of the first cryoadipolysis device for the reduction of undesired subcutaneous fat by the FDA in 2010 (K080521), many studies have confirmed the efficacy and safety of this non-invasive technique, both *in vitro and in vivo*[2-4].
Moreover, various clinical trials have confirmed that it is a safe technology which causes minimal pain and guarantees a quick recovery for patients[1].
Cooltech® and Cooltech Define are among the world's leading cryoadipolysis platforms in this regard.
In previous studies, we have recreated the Cooltech procedure using numerical simulation with COMSOL Multiphysics®; simulations have proved to be an excellent tool for improving understanding of the cryoadipolysis process and for optimizing applicator design for better efficacy and safety[5,6].
These simulations have previously been validated using in-vitro experiments[7].
However, there is one aspect of cryoadipolysis that cannot be observed through in-vitro experimentation and therefore has barely been studied: ischemia[4]. Local ischemia (decreased blood flow inside suctioned tissue) is caused by the vacuum suction of the applicators when cryoadipolysis is performed.
Since even a small decrease in the percentage of blood flow produces important changes in the thermal behavior of tissue, ischemia during cryoadipolysis may have significant consequences on the efficacy of treatment. We developed a mathematical model of ischemia based on the applicator geometry and suction pressure[6].
Here, we performed a preliminary clinical validation of our *in-silico* model of the cryoadipolysis method that includes a model for ischemia.
A thermocouple probe was introduced into the fatty tissue during a cryoadipolysis procedure, to monitor internal temperature. Subsequent experimental data were compared with the results of simulations.
A more accurate *in-silico* model that includes blood perfusion will serve to improve the design of the Cooltech cryoadipolysis procedure, in order to provide maximal efficacy and safety for subjects.

Materials and methods

In-silico model

The *in-silico* model simulating the physics of the heat exchange between the biological tissues and the Cooltech® device was created with the COMSOL Multiphysics® software using the finite elements method[5-7].
The meshed geometrical domains consisted of the biological tissues involved (skin and fat) and the cryoadipolysis applicators (*Figure 1A*). Applicators were designed using SolidWorks® software; designs were then imported to the COMSOL Multiphysics® software (*Figure 1B*). The simulation was conducted by solving the equation of heat transfer for biomaterials (*Eq 1*):

A. $$\rho C_p \frac{\partial T}{\partial t} + \nabla \cdot q = Q + Q_{bio}$$

B. $$q = -k \nabla T$$

C. $$Q_{bio} = \rho_b C_{pb} \omega_b (T_b - T) + Q_{met}$$

Equation 1 *- A: Equation of heat transfer for biomaterials; B: Heat flux by conduction in the tissue and C: Biological heat. Parameters and variables of the equations: ρ: density of the tissue; C_p: specific heat at constant pressure of the tissue; ∂T/∂t: partial derivative of the temperature (T) with respect to the time (t); ∇: mathematical operator Nabla (operator that applies partial derivatives in space to a magnitude); q: heat flux by conduction in the tissue; Q: heat source; Q_{bio}: biological heat; k: coefficient of heat conductivity; ρ_b: blood density; C_{pb}: blood specific heat at constant pressure; ω_b: blood perfusion rate; T_b: arterial blood temperature; Q_{met}: metabolic heat source.*

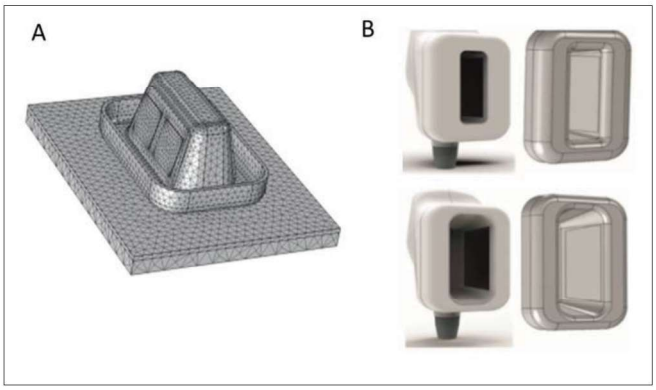

Figure 1 *- (A) Mesh used for the heat transfer equation resolution by finite domains method (Straight HP case). (B) Tight design (top) and Straight design (bottom) of Cooltech applicators.*

For each material used in the simulation, three basic parameters were required: (1) specific heat (C_p), (2) thermal conductivity (k), and (3) density (ρ).
The materials used in the simulations were fat, skin, the polypropylene of the applicator's outer body, the anodized aluminum of the cooling plates' surface and the anodized aluminum of the cooling plates [8-11] (*Table 1*). Four parameters were required to simulate blood perfusion: (i) blood temperature (T_b), (ii) blood-specific heat capacity at constant pressure (C_{pb}), (iii) blood density (ρ_b), and (iv) blood perfusion rate (ω_b) in fat and skin[12,13] (*Table 2*).

Material	Cp (J/kg·K)	k (W/m·K)	ρ (kg/m³)
Fat [8] *T in oC	$1984.2 + 1.4733T - 4.8008 \cdot 10^{-3}T^2$	$0.18071 - 2.7604T \cdot 10^{-4} - 1.7749 \cdot 10^{-7}T^2$	$925.59 - 0.41757T$
Skin [9]	3391	0.37	1109
Plastic (Polypropylene) [10]	1800	0.16	1040
Anodized Aluminum [11]	880	18	2700
Aluminum [9]	900	238	2700

Table 1 *- Required physical parameters to solve the heat transfer equation.*

Blood Temperature	36 (ºC)
C_p blood[12]	3220 (J/kg·K)
ρ blood [12]	900 (kg/m³)
ω in fat [13]	$4.2 \cdot 10^{-4}$ (1/s)
ω in the skin [13]	0.0018 (1/s)

Table 2 *- Required physical parameters to simulate blood perfusion.*

The different stages of a cryoadipolysis treatment were recreated with the simulations, including the cooling of tissues through contact with cooled aluminum plates, the use of cryoprotectant on the skin and the ischemia produced by the suction of the tissues into the applicators. Regarding the original conditions of the simulations, the initial temperature was 36ºC for biological tissue (simulating body temperature) and 20ºC (room temperature) for all other materials.
As a first boundary condition, an isolated system was considered, which means that there was no heat flow in its contours (*Figures 2A and 2B*).
As a second boundary condition to simulate the cooling process, a time-dependent temperature was applied to the aluminum plates.
Aluminum plates, which in a real-life situation are cooled by Peltier cells, do not achieve a cold temperature instantaneously and require some time to reach the set temperature (-8ºC with the Cooltech® device). We incorporated the temperature drop function of the Cooltech applicators in the simulation (*Figure 2C*).

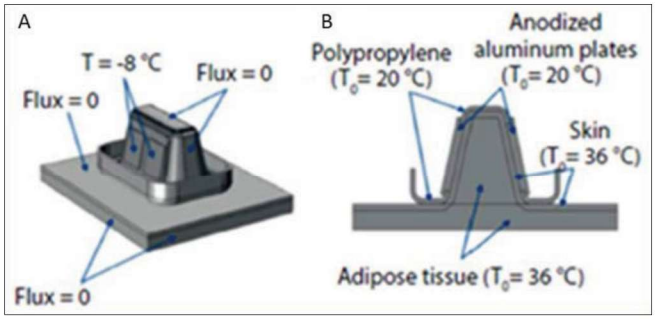

Figure 2 *- (A) Boundary conditions and (B) initial conditions used during simulations.*

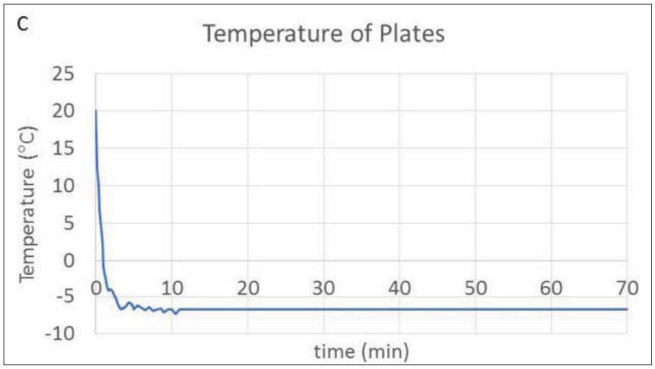

Figure 2 *- (C) Temperature curve of aluminum cooling plates as a function of time. Abbreviations: T, temperature; oC, degrees Celsius.*

In order to simulate the suction effect of the applicator on the tissue to be cooled, the treated biological tissue was divided into two parts: (i) the suctioned tissue, consisting of skin and fat inside the applicator, and (ii) the non-suctioned tissue, consisting of the skin and fat adjacent to the suctioned tissue. Assuming partial ischemia, a model was proposed to estimate a blood perfusion factor (BPF) [6] (Eq 2).

$$BPF = 1 - e^{-\left(k \times \frac{Width\ of\ the\ applicator\ cavity}{Suction\ pressure \times Angle\ of\ cooling\ surfaces \times Depth}\right)}$$

Equation 2 *- Equation for the blood perfusion factor.*

where *e* is a mathematical constant with an approximate value of 2.71828 and is the base of the natural logarithm, and k is a constant to determine the perfusion factor for each applicator, obtained by applying the model to a reference value[6]. The following premises were also considered in order to develop the model:
a) BPF of between 0 and 1, multiplying the blood perfusion frequency (ω) of the biological tissue in its natural state. Without ischemia, the factor is 1 and there is natural biological heat; with 100% ischemia, the factor is 0 and biological heat is null.
b) BPF increases with the blood perfusion surface (surface of the suctioned tissue through which blood flows).
c) BPF decreases with the depth and the inclination angle of the lateral surfaces inside the applicator, and with suction pressure.
d) For high BPF values (low ischemia), changes in the

design parameters do not significantly affect ischemia. On the other hand, for low BPF values (high ischemia), small design changes can significantly affect the resulting ischemia.
For the Tight and Straight Cooltech applicators, the perfusion factor was estimated at 0.31 and 0.42, respectively[6].

Clinical procedure

In order to compare simulated results with clinical data, two subjects with localized adipose tissue in the abdominal area were recruited. The study was conducted in compliance with the principles set forth in the current version of the Declaration of Helsinki, Good Clinical Practice, and the laws and regulatory requirements for the use of medical devices in Spain. Both subjects were consulted, provided their consent and clearly understood the procedure before the study. All procedures fulfilled Organic Law 15/1999 on the Protection of Personal Data and Regulation (EU) 2016/679 of the European Parliament and the Council of April 27 2016, concerning the protection of natural persons with regard to the processing of personal data and the free circulation of said data. Both subjects were treated with the Cooltech device, one with a Straight applicator (Subject 1) and the other with a Tight applicator (Subject 2) (*Figure 3A*).
Prior to the treatment, a thermocouple probe (generic K-type thermocouple) was introduced through a cannula reaching the dermal fat layer through a dermal incision. The probe was connected to a GM1312 Dual-Channel LCD Digital Thermometer to track the temperature during cryoadipolysis treatment (*Figure 3B*).
The cryoadipolysis treatment began with a suction test to ensure the suitability of the applicator for the fatty tissue to be treated. A cryoprotectant CGP (Cool Gel Pad) membrane was then placed on the area to protect the epidermis and dermis. The applicator was positioned over the CGP and then activated. Suction was set at 240 mbar and the temperature at -8ºC.
After 70 minutes of treatment, the applicator was removed along with the CGP membrane and a massage was performed on the treated area.
After the treatment, the depth and position of the probe was verified by palpation and by ultrasound with a Mindray M5 ultrasound system (*Figure 3C*). The simulation was performed at the same x, y and z coordinates of the simulated tissue.

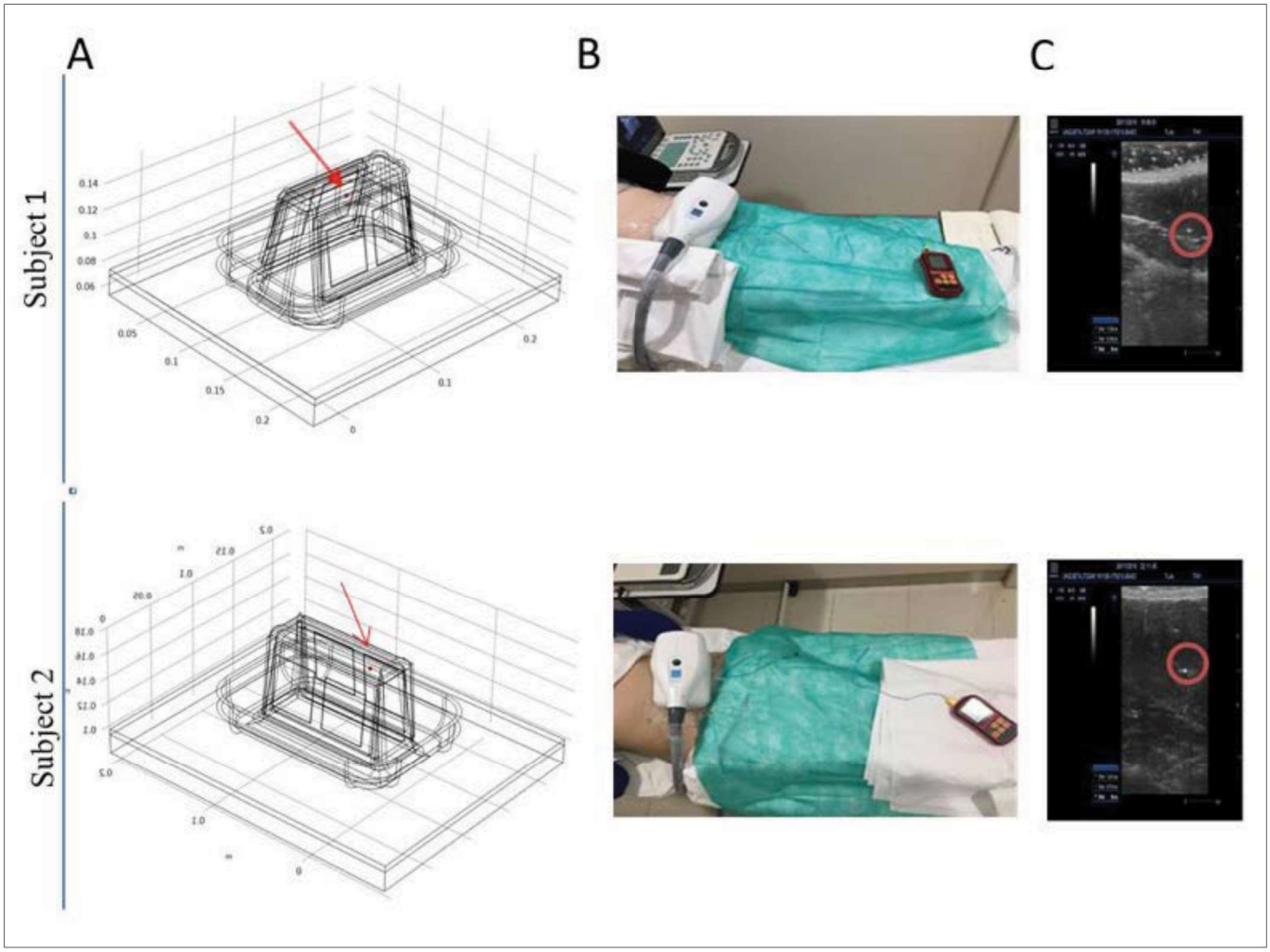

Figure 3 *- (A) Point evaluated in the simulation. (B) Treatment images with thermocouple probe attached for Straight applicator (Subject 1) and Tight applicator (Subject 2). (C) Ultrasound images of the treated tissues. Probe position inside the tissue is marked in red.*

Statistics

In order to evaluate the correlation between simulated and observed results, the coefficient of determination (R2) has been computed. The variance of the difference between both data sets and the maximum value of the difference is also shown.

Results

We described the temperature obtained from the clinical observations during cryoadipolysis as a function of time, and we compared the obtained results with the outcome of the simulations, which took into account ischemic processes. In the case of Subject 1 (treated with a Straight applicator), the experimental data closely matches the data obtained from the simulation. In this case, the greatest discrepancy between the experimental data and the data obtained from the simulation was - 2.21ºC at 10 min. The variance of the difference was 1.01ºC and R2 was 97.87% (*Figure 4A*).
Similarly, in the case of Subject 2 (treated with a Tight applicator), the experimental data matches the data obtained from the simulation very well, with a maximum difference of -2.92ºC at 20 min. The variance of the difference is 1.09ºC and the coefficient of determination (R2) is 99.08% (*Figure 4B*).

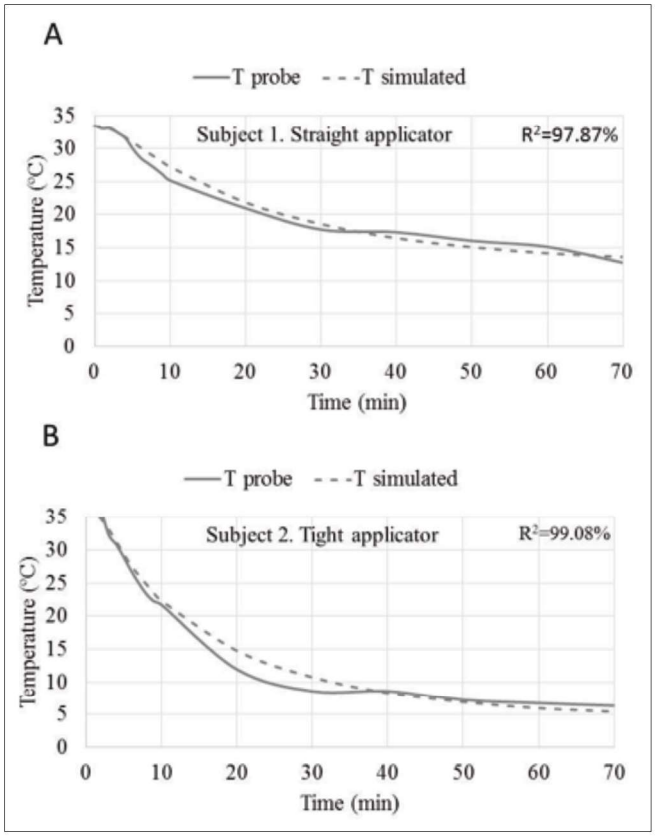

***Figure 4** - Experimental Temperature versus Simulation data for Subject 1 (A) and Subject 2 (B).*

Discussion and conclusions

During a cryoadipolysis procedure, ischemia (reduced blood perfusion) is caused in the treated area due to it being sucked into the applicator[4]. Decreased blood flow in the suctioned tissue leads to a reduction of biological heat (Qbio), which does indeed have a great influence on the cooling dynamic of the cryoadipolysis procedure. In contrast, the metabolic heat (Qmet) of each tissue (Eq 1C) is considered to be negligible during cryoadipolysis[12,13]. Therefore, the 3D heat transfer *in-silico* model used in this study considers ischemia as the only parameter for determining biological heat.
Accordingly, the efficacy of cryoadipolysis does not depend solely on tunable parameters (i.e. temperature, pressure) but is also affected by the geometry of the selected applicator. The shape of the applicator determines the contact surface and the amount of tissue to be treated along with the induced ischemia, thus directly influencing bodily thermal response.
We have validated the described 3D *in-silico* model using two applicators that differ in shape. The correlation between the theoretical data, obtained by means of simulation, and the clinical data obtained during cryoadipolysis administered to two subjects with the Straight and Tight applicators, was 97.87% and 99.08%, respectively. The maximal reported difference was less than 3ºC. Notably, we can confirm that the Tight applicator provides better treatment efficacy. This is due to its long and narrow design, which provides an elevated contact area with the skin and therefore better cooling of the fat volume lodged inside[5].
In conclusion, this experimental study has proven that it is possible to generate mathematical models enabling the simulation of the cooling dynamics of Cooltech® applicators. We have created a realistic model by determining the relationship between the ischemia produced in the suctioned tissue within the applicator and the geometry of said applicator. This information has no precedents and contributes great value to existing clinical experience.
More studies should be performed, considering a variety of different applicators; the number of subjects should also be increased. Confirmation of results would result in a fully validated method for determining the extent of cooling generated by cryoadipolysis applicators by means of numerical simulations that are only dependent on their geometric parameters. This may lead to the design of more effective cryoadipolysis procedures, primarily in terms of patient safety.
A validated *in-silico* model may also substantially reduce the need for clinical subjects to validate new device designs, thus clearly providing a significant added value.

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Conflict of interest

The authors of this publication conduct research in Cocoon Medical S.L.U., a company which is developing products related to the reported study. However, this publication strictly adheres to objectivity and ethical principles for independent research.

REFERENCES

1. Viera G, De Los Llanos M, Oliva J, Giménez C. Efficacy and Safety of Subcutaneous Fat Reduction by Cryoadipolysis. *IRJPMS.* 2019; 3(2):38–43.

2. Preciado J, Allison J. The effect of cold exposure on adipocytes: Examining a novel method for the noninvasive removal of fat. *Cryobiology.* 2008; 57:327.

3. Manstein D, Laubach H, Watanabe K, Farinelli W, Zurakowski D, Anderson RR. Selective cryolysis: A novel method of noninvasive fat removal. *Lasers Surg Med.* 2008; 40(9):595–604.

4. Avram MM, Harry RS. Cryolipolysis for subcutaneous fat layer reduction. *Lasers Surg Med.* 2009; 41(10):703–8.

5. Viera G, Villena J, García P, Khrystova K, Colina M. A Comparative Study of Cooltech® Handpieces for Cryoadipolysis Using Numerical Simulation. *Probl Cryobiol Cryomed.* 2018; 28(4):343–356.

6. Viera G, Villena J. New Cooltech Define® Cryoadipolysis Applicators: A Scientific and Comparative Study with Cooltech® Applicators. *EJMI.* 2019; 3(2):85–94.

7. Viera G, García P, Villena J. Validation of Cooling and Freezing Dynamics of Cooltech® Using an Experimentally Adjusted Physical Model. *SAS J Med.* 2017; 3(12):343–9.

8. Pham QT. Food freezing and thawing calculations. SpringerVerlag New York; 2014. XV, 153.

9. COMSOL Multiphysics® Modeling Software [Internet]. [cited 2018 Sep 7]. Available from: https://www.comsol.es/

10. Thermal Expansion Properties of Materials [Internet]. Vol. 10, Online. 1900 [cited 2018 Sep 14]. p. 225–32. Available from: https://www.professionalplastics.com/professionalplastics/ThermalPropertiesofPlasticMaterials.pdf

11. Alumina ceramic (94% alumina) [SubsTech] [Internet]. Available from: http://www.substech.com/dokuwiki/doku.php?id=alumina_ceramic_94_alumina

12. Raulin C, Karsai S. Laser and IPL technology in dermatology and aesthetic medicine. *Springer.* 2011; 1:419.

13. Williams LR, Leggett RW. Reference values for resting blood flow to organs of man. *Clin Phys Physiol Meas.* 1989; 10(3):187–217.