Treatment of cutaneous vascular and pigmentary injuries using laser: evaluation of effectiveness and tolerance of Cytolnat Centella cream during post-operative care for cicatrisation purposes.

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1 - Introduction

Skin colour changes, either established as erythrocouperose or lentigines or provoked as tattoos, are badly felt notwithstanding their benignant nature. Since a few years, treatments using vascular lasers (KTP or pulsed dye type) or pigmentary lasers (Q-switched Nd:YAG type), are frequently used. Their effectiveness is certain, but they cause well detailed side effects, sometimes visible, that may require restraining from social life for some days.

In both cases, immediate post-operative occurrences are well known and expected: burning or tensing sensation, erythema, oedema, crusts, and transudation. These require local care for some days, namely application of a cream capable to keep undesired symptoms under control to bring relief to the patient and favour cicatrisation.

The main goal of this study is to evaluate the effectiveness of Cytolnat Centella cream used during post-operative care for its soothing and repairing effects in patients suffering from pigmentary or vascular injuries following laser treatment. Evaluation of clinical tolerance and cosmetic acceptability constitutes a secondary objective.

2 - Material and Methods

Nine dermatological investigators evaluated the activity of Cytolnat Centella cream during an open multi-centre clinical study of phase IV with direct individual benefit, whose protocol received a favourable opinion from the Consultation Committee for Individual Protection in Biomedical Research "CCPPRB" (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of Bordeaux Hospital Centre. Before being included, all patients were advised of the characteristics of the study and signed an informed consent sheet.

2.1 - Inclusion Criteria

The study included male and female patients, from 18 to 75 years of age, showing either erythrocouperose in stage 1 to 4 or pigmentary injuries (lentigines, *café-au-lait* marks on the
back of the hands or face, or tattoos) and due for treatment with vascular laser (KTP or

pulsed dye type) in the case of vascular injuries, or with pigmentary laser (Q-switched Nd:YAG type) in the case of pigmentary injuries.

2.2 - Exclusion Criteria

The following patients were excluded: patients suffering from dermatosis extending or that may extend to the area to be treated, severe chronic or progressive diseases, known intolerance to any of the components of the product under study; patients undergoing corticotherapy or being treated with NSAIDs or anticoagulants; patients having known keloid cicatrisation antecedents; and pregnant or nursing women.

2.3 - The Product under Study: Properties and Directions for Use

Cytolnat Centella cream results from the combination of an oil/water emulsion with filmogenic, soothing and moisturising properties that favour crust-free cicatrisation, and a purified titrated extract of Gotu Kola *(Centella asiatica)* containing 60% asiatic and madecassic acids and 40% asiaticoside. Gotu Kola extract constituents contribute to mobilisation of the biochemical and enzymatic antioxidant biological systems that the skin uses to fight against oxidative stress caused by solar or ionising radiation burns or sores. Furthermore, it enhances the cicatrisation repairing process by stimulating biosynthesis of extra-cellular matrix constituents (collagen and glycosaminoglycane), as well as revascularization.

At the end of the laser session, the investigator performs the first application of a thick layer over the treated area. In the evening of the operating day and for seven days thereafter, the patient applies the cream by means of a light massage until complete penetration, as follows: 4 to 6 applications the first two days, 2 to 4 applications per day the following five days. All through the period of study, making-up is absolutely forbidden to patients exhibiting facial injuries.

2.4 - Effectiveness Evaluation Criteria

Intensity of erythema- or oedema-induced pain was rated using an analogue visual scale with intermediate reference points (light, moderate, strong) both by the investigator at the end of the laser session (D0M) and during the visit at the end of the study (D8), and by the patient every day, in the morning (D1M to D7M) and in the evening (D0E to D7E), before the first and last applications.

The presence or not of transudation and crusts was evaluated by the patient every day, morning and evening, before the first and last applications, and by the investigator during the visit at the end of the study.
At the end of the study, global judgements on effectiveness given by the investigator and by the patient were appraised using a 4-step scale: nil, light, remarkable, and very remarkable.
The number of per-day applications of the product under study was registered by the patient every day, from the day of the laser session to the last day of treatment.

2.5 - Tolerance Evaluation Criteria

Tolerance was appraised every day by the patient on the basis of the appearance of side effects, namely of allergic or irritating nature, such as itching and eczematisation.
At the end of the study, global judgements on tolerance given by the investigator and by the patient were appraised using a 4-step scale: bad, rather good, good, and very good.

2.6 - Acceptability Evaluation Criteria

Cosmetic acceptability of the product under study was appraised by the patient at the end of the study according to ease of application and penetration, soothing effect, agreeable or disagreeable texture and odour.

2.7 - Statistical Methodology

Comparison of average values was carried out using Student's *t*-test with a probability threshold of $p \leq 0.05$. When the sample size exceeded 30, reduced normal law was used for unilateral and bilateral tests as well (epsilon = 1.64 and 1.96, respectively).

Kinetics of disappearance of signs, pain, erythema, and oedema was quantified by comparing the respective average value "m" of the rating obtained on each expiry, as follows:

1) on one side, by comparison with the value "m_o" obtained at D0M to determine the expiry starting from which the difference became significant (TS);
2) on the other side, by comparison with "$m_o/2$" to determine the expiry starting from which sign rating decreased by 50% relative to D0M in a statistically significant manner (T50%).

The effects of the 2 laser types were also compared by comparing average values on each expiry with reference to a certain sign to determine the lapse of time during which there exists a significant difference.

The correlation between reduction of effects on erythema and oedema "y" and the number of per-day applications "x" was studied using linear regression (method of least squares). Linearity of regression type:

$$y = ax + b$$

was tested on one side by applying Student's *t*-test on slope "a" of the straight line (significance relative to "0"), and on the other side by determining the correlation factor "r".
Determination of the effective dose 50 (ED50), *i.e.* the dose enabling a 50% reduction of the sign "y_o" measured at D0M, was calculated starting from the equations of regression straight lines obtained with a value of "y" equal to "$y_o/2$".

For the parameters: transudation, crusts and undesirable effects, a percentage was calculated in relation to the population considered.

3 - Results

3.1 - Population under Study

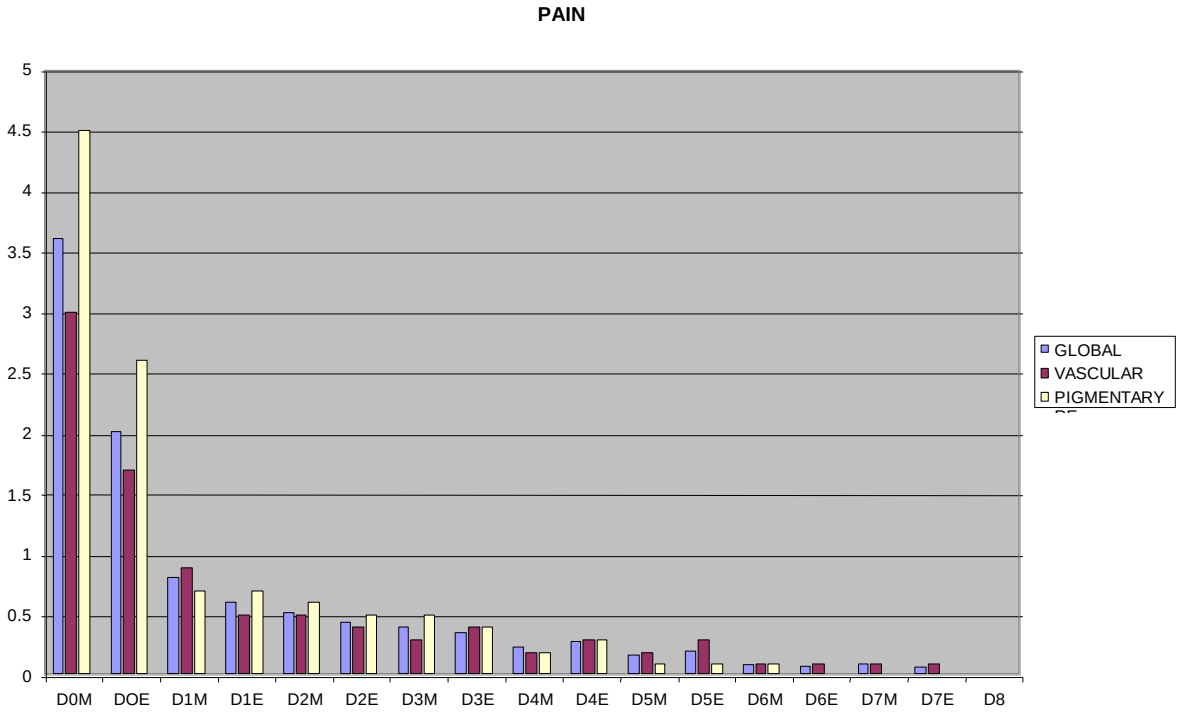
	No. of patients	WOMEN	MEN	AVERAGE AGE
TOTAL	70	58, *i.e.* 82.9%	12, *i.e* 17.1%	49.8 (2.7)
PIGMENTARY LASER	29*, *i.e.* 41.4%	24	5	51.1 (2.8)
VASCULAR LASER	41**, *i.e.* 58.6%	34	7	48.9 (2.6)

70 patients were included in this study, of which 12 of male sex and 58 of female sex, aged averagely 49.8 years.
41 (58.6%) exhibited erythrocouperose (with average severity index: 2.9) treated with vascular laser; 29 (41.4%) exhibited pigmentary injuries, of which four tattoos, treated with pigmentary laser.

3.2 - Effectiveness Evaluation

Pain initially is not strong rating 3.6 on a 10-step scale, even though significantly stronger after pigmentary laser; then it decreases rapidly (significant difference relative to D0M starting from the 12^{th} hour) with a reduction by minimum 50% in 24 hours, and

disappears completely at the end of the study. This trend is exactly the same with both laser types, vascular and pigmentary.



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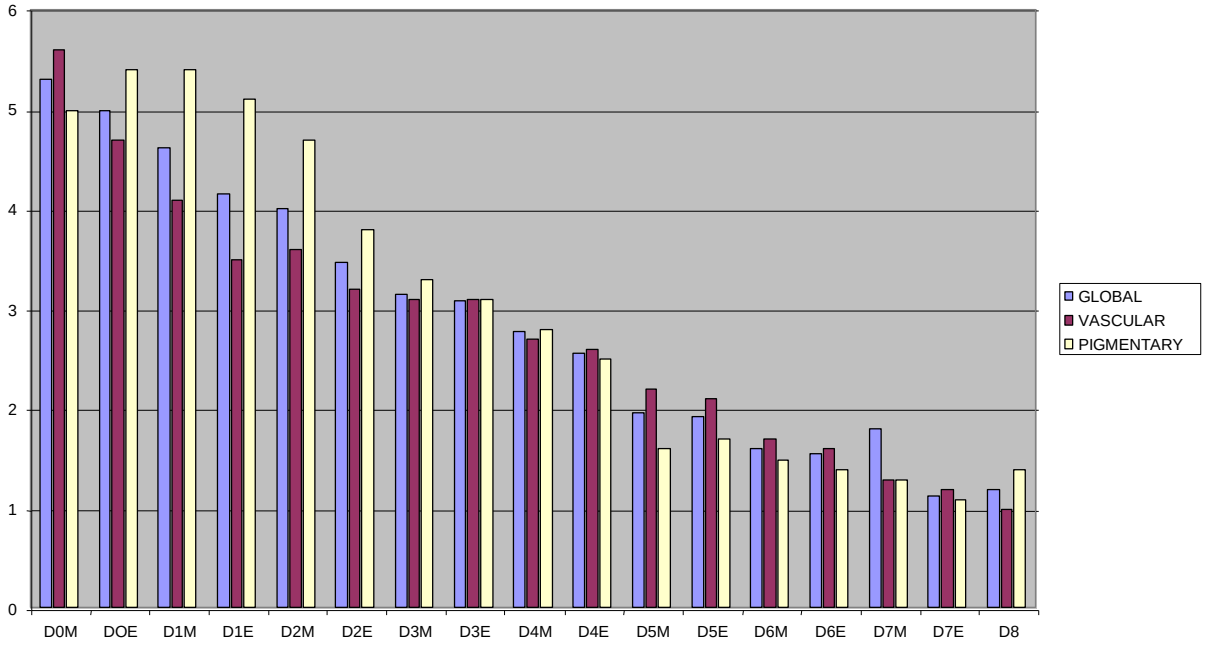
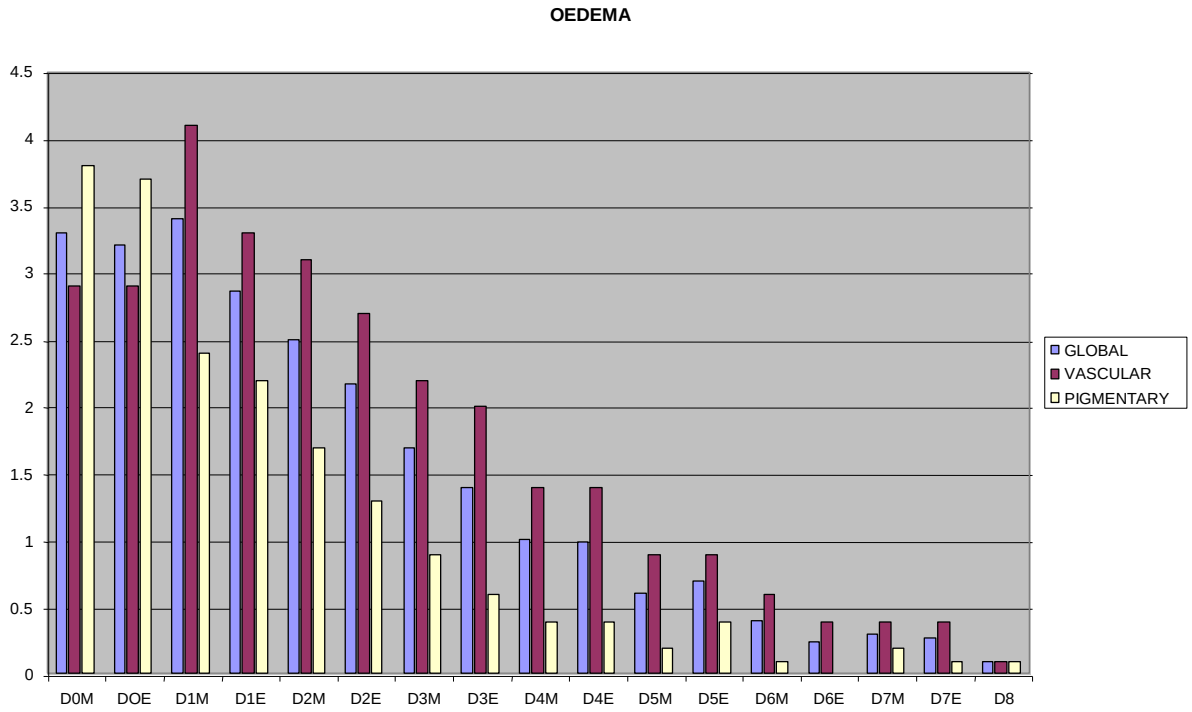
Erythema is initially moderate rating 5.3 on a 10-step scale, then it decreases rather rapidly with a significant difference relative to D0M starting from the 24th hour. The reduction is equal to 50% at D3E with almost complete disappearance at the end of the study. Erythema resulting from treatment with either laser type is statistically comparable, but regression proves slower in the case of vascular laser; the difference remains significant from D1M to D2M, that is in 24 hours.

ERYTHEMA

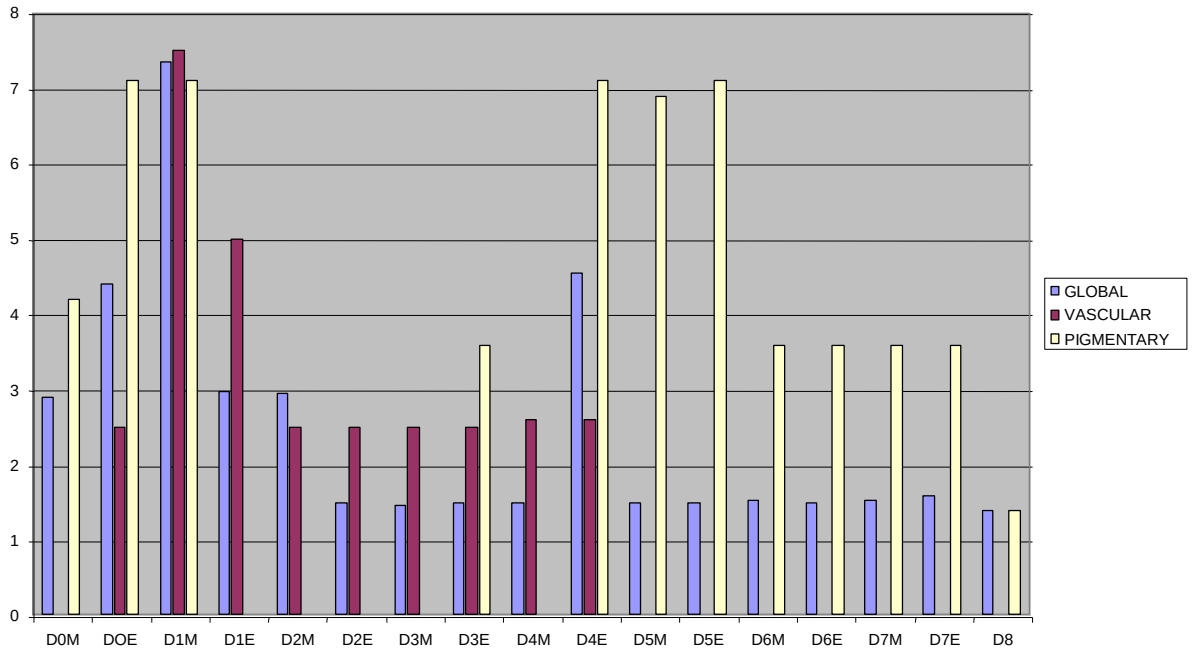

6
5
4
3
2
1
0
D0M
DOE
D1M
D1E
D2M
D2E
D3M
D3E
D4M
D4E
D5M
D5E
D6M
D6E
D7M
D7E
D8
GLOBAL
VASCULAR
PIGMENTARY

Oedema initially is not remarkable rating 3.3 on a 10-step scale, then it rapidly decreases in 48 hours (expiry when the difference is significantly lower relative to D0M) with a 50% reduction at D3E and almost complete disappearance at the end of the study. Initial oedema (D0M) resulting from treatment with pigmentary laser is maximum and statistically more relevant (rating 3.8) than that caused by vascular laser (2.9). Here, however, the acme (4.1) with intensity similar to pigmentary laser is achieved only 24 hours later and this may explain why regression is noticeably slower (the difference relative to pigmentary laser remains significant from D1M to D5M, that is during 4 days).

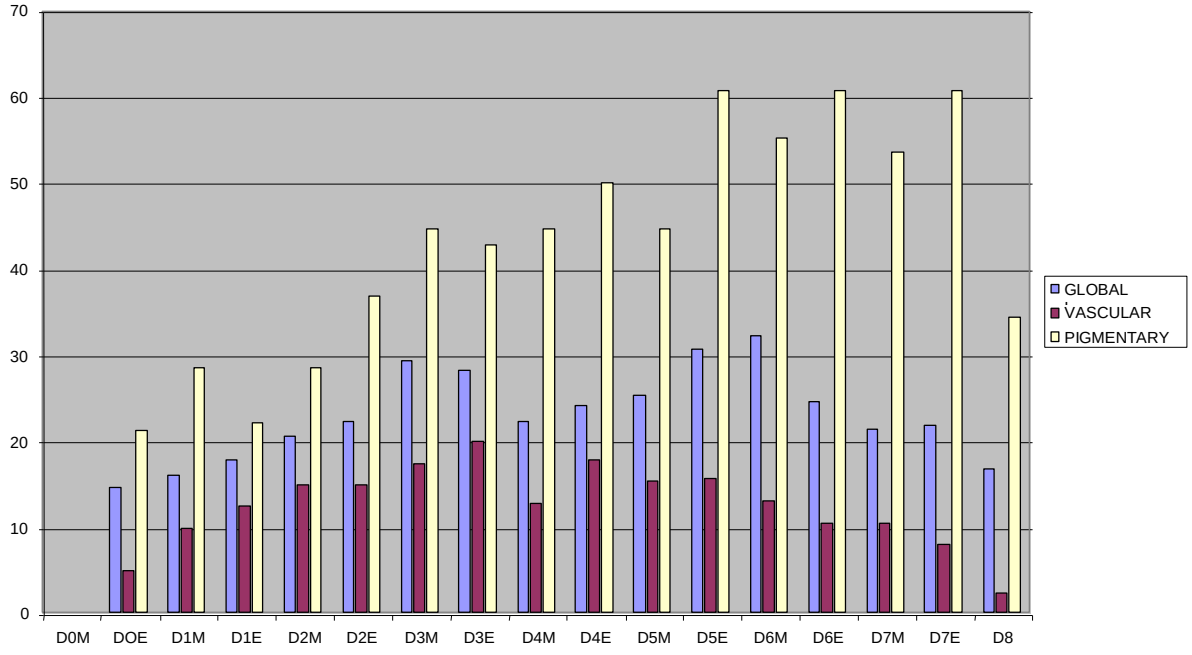


Transudation and crusts are more important after pigmentary laser treatment. Transudation rate arrived at 7.1% after 24 hours and then down to 3.6% the 7th day; crust rate arrived at 60.7% the 5th day with regression to 34.5% during the final evaluation made at D8 by the experimenter. After vascular laser, maximum transudation occurs after 24 hours rating 7.5% and decreases to nil the 4th day; maximum crust rate equal to 20% occurs the 3rd day and decreases to 8% at the end of the study.

TRANSUDATION PERCENTAGE

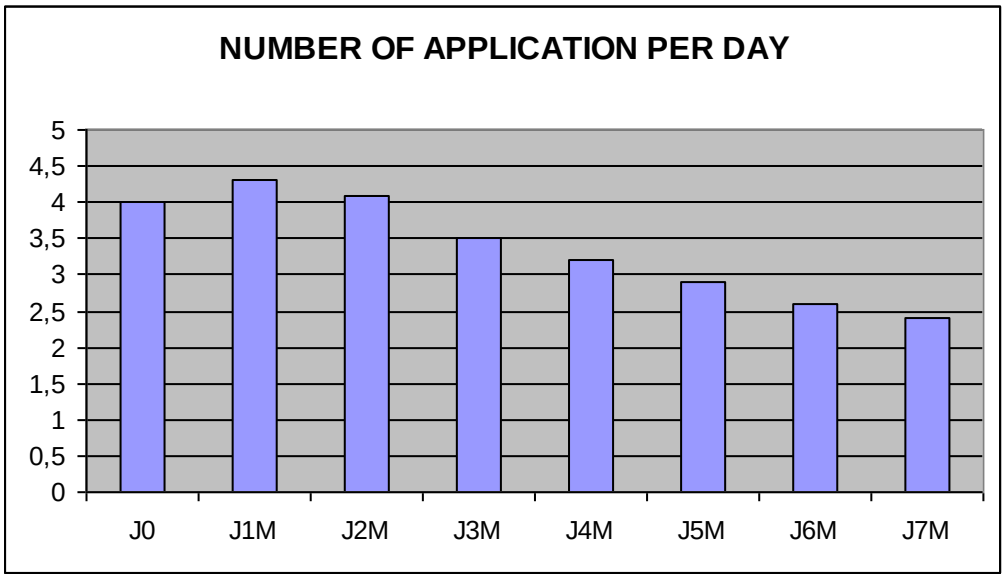


CRUST PERCENTAGE



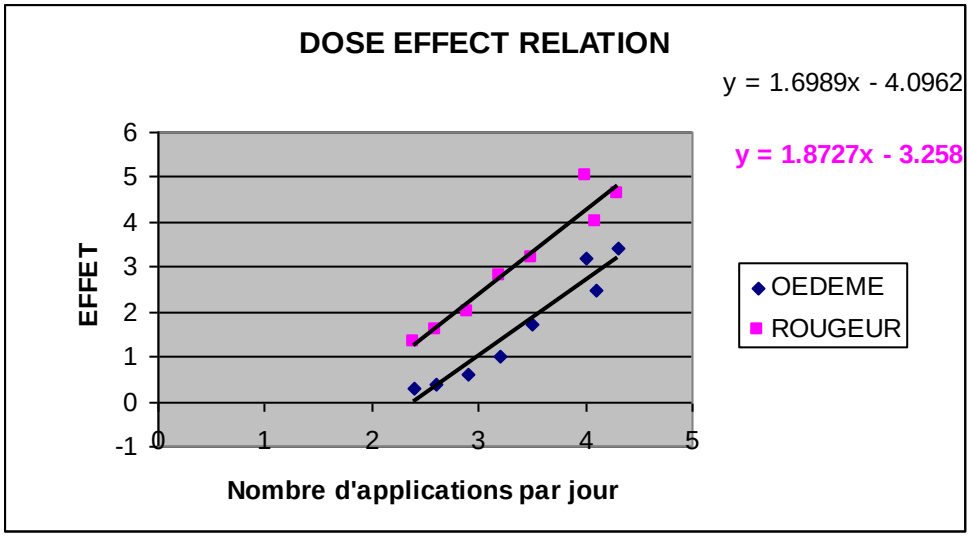
Global judgements on effectiveness given by the investigator and the patient are similar and range from satisfactory to very satisfactory with average index = 3.7 and 3.6 when 4 corresponds to maximum satisfaction.

The number of per-day applications of the product under study decreases concurrently with the reduction of erythema or oedema.



Therefore, it seemed opportune to study the correlation, if any, between each of these 2 parameters and the number of per-day applications in order to establish the existence of a relation between dose and effect (fast pain reduction does not allow this study).

EFFECT	correlation equation y = ax + b	r	P	ED 50
OEDEMA (global)	**y = 1.7x - 4.1**	**0.967**	**9 E-05**	**3.35**
OEDEMA (vascular laser)	y = 1.84x - 4.25	0.983	1.20E-05	3.1
OEDEMA (pigmentary laser)	y = 1.51x - 3.91	0.832	0.01	3.8
ERYTHEMA (global)	**y = 1.87x - 3.26**	**0.968**	**0.003**	**3.07**
ERYTHEMA (vascular laser)	y = 2.05x - 4.23	0.944	0.0004	3.22
ERYTHEMA (pigmentary laser)	y = 2.37x - 4.74	0.976	3.3 E-05	3.14


DOSE EFFECT RELATION
y = 1.6989x - 4.0962
y = 1.8727x - 3.258
EFFET
6
5
4
3
2
1
0
-1
0
1
2
3
4
5
Nombre d'applications par jour
OEDEME
ROUGEUR

The study of linear regression for both erythema and oedema shows that linearity of the clinical response (y) depending on the number of per-day applications (x) is accepted with excellent probability (p). The calculation of the effective dose 50 (ED 50, the dose that decreases initial intensity of erythema or oedema by 50%) gives values ranging from 3 to 4 applications per day for both erythema and oedema.
Notwithstanding the differences observed, the same study conducted for each of the 2 laser types does not lead to clinically different results.

3.3 - Tolerance Evaluation

There was no study issue that could be blamed on a tolerance problem. The only undesirable effect was assessed in an ectopic female patient who exhibited slight itching for 3 days after applications.
Global judgements on tolerance given by the investigator and by the patient, are similar and ranges from good to very good with average index = 3.8 and 3.7, respectively, when 4 corresponds to maximum satisfaction.

3.4 - Acceptability Evaluation

100% of the patients were satisfied or very satisfied with the ease of application and texture of the cream
90% of the patients found penetration easy and fast, felt a sensation of well being after application and found the smell agreeable.

	Ease of application	Ease of penetration	Soothing effect	Texture	Odour
Experimenter's evaluation at D8	1	0.9	0.9	1	0.9
Patient's self-evaluation D7S	1	0.9	0.9	1	0.9

4 - Discussion

The aim of this study is to evaluate in open Cytolnat Centella cream effectiveness when applied locally for seven days to treat immediate post-operative follow-ups in patients exhibiting pigmentary or vascular injuries after laser treatment.
The analysis of results recorded on a daily basis by means of self-evaluation shows fast disappearance of pain, which decreases by 50% in 24 hours.

Globally, erythema or oedema reduction is fast, significant after 24 and 48 hours from treatment respectively, and down to 50% of its initial value in 3.5 and 3 days, respectively.

INFLAMMATION SIGN KINETICS					
PAIN		ERYTHEMA		EDEMA	
TS vs. D0	T 50%	T S vs. D0	T 50%	T S vs. D0	T 50%
D0E	D1M	D1M	D3E	D2M	D3M
12 hrs	**24 hrs**	**24 hrs**	**3.5D**	**48 hrs**	**72hrs**

T s vs. D0 = time to achieve a significant difference (p=0.05) relative to T0
T 50% = time to achieve a 50% reduction of the effect relative to T0

As expected, a noticeably slower cicatrisation was observed in the case of pigmentary laser treatments (1/3 of crusts at D8) compared to that obtained using vascular laser (8% of crusts at D8). This should be put in relation with the laser operating mechanism and different target tissue to be treated.

The relation with the dose is clear with the effective dose 50 ranging between 3 and 4 applications per day.

The average global judgements on effectiveness given by the investigator and by the patient are satisfactory-very satisfactory.

Therefore, the use of Cytolnat Centella cream allows a better post-operative course, after either vascular or pigmentary laser treatment. Repeated application of this cream enabled side effect reduction and shorter cicatrisation time. Galenic formulation of this cream and its perfect tolerance allow repeated usage and make it a low-demanding treatment.

5 November 2003