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Efficacy of combining Micronized Silver, Zinc Acetate and Lauric Acid in mild-moderate acne

Summary

Acne is a multifactorial inflammatory disease in which P. acnes assuredly plays a key role. Though it is not an infectious disease, antibiotics are used to reduce the P. acnes load and for their anti-inflammatory action. The common use of oral antibiotics concurrently with topical antibiotics has increased the phenomenon of antibiotic resistance. This problem occurs both with the pathogenic agent of acne and also with infectious agents, such as certain strains of S. aureus, coagulase negative Staphylococci and A group Streptococci, that cause serious infections, such as MRSA and infections in the upper airways. Hence, therapeutic failure does not only occur in the case of acne but also towards other important infections in other organs. This has encouraged studies to seek anti-inflammatory therapies that do not develop resistances, such as the combination of Micronized Silver, Zinc Acetate and Lauric Acid, and which have an anti-inflammatory and antibacterial action. In our study we administered this combination as treatment to a group of 20 patients (Group A) presenting slight-moderate acne + a specific cleansing agent for acneic skin containing Taurates, Silver Citrate and microspheres of Silicon, and treated Group B made up of 20 patients presenting slight-moderate acne with the same combination + a non-specific cleansing agent for acneic skin. The combination of Micronized Silver + Zinc Acetate + Lauric Acid is effective in reducing acneic lesions, both inflammatory and non-inflammatory, in both treated groups. The statistically significant reduction is more enhanced for inflammatory lesions.

Key words: Acne, Micronized Silver, Zinc Acetate, Lauric Acid.

Introduction

Antibiotic therapy has been extensively used for the treatment of acne to reduce the P. acnes load and for its anti-inflammatory action. The widespread use of oral antibiotics started in 1960 but signs of antibiotic resistance occurred only in the mid-70s after topical antibiotics were introduced for slight-moderate acne therapy. In 1979 Crawford et al. described early signs of resistance shown by P. acnes towards erythromycin and clindamycin. In 1983 Leyden et al. were the first to report resistance to tetracyclines. Several other studies followed between 1992 and 2001, proving that resistance to erythromycin and to clindamycin was more frequent than to tetracyclines, and the concurrent use of topical and systemic antibiotics increases the possibility of developing antibiotic-resistance. Resistance does not only develop against the pathogenic agent of acne but also against certain strains of S. aureus, coagulase negative Staphylococci and infections in the upper airways. Hence, the therapeutic failure in cases of acne and, especially, towards other important infections of other organs.

Increase in P. acnes resistance to antibiotics

Progress of the percentage of bacterial resistance over the years.
International guidelines for the prevention of bacterial resistance.

CONSENSUS: Strategies to limit antibiotic resistance are important in acne management

Level of evidence: V
- Treatment regimens that limit, or even reduce, the incidence of bacterial antibiotic resistance are recommended.
  - Selection pressure can affect other, more pathogenic bacteria in addition to P. acnes.
  - High rates of resistance have been correlated with high outpatient use of antibiotics.
- Use of oral antibiotics can lead to resistance in commensal flora at all body sites; topical antibiotics lead to resistance largely confined to skin of reated site.
  - Oral antibiotics are recommended for moderate to moderately severe acne.
  - Topical antibiotics may be used in mild to moderate acne as long as they are combined with benzoyl peroxide (BPO) and a topical retinoid.
  - Limit the duration of antibiotic use and assess response to antibiotics and continuing need at 6 o 12 weeks.
  - Some countries have regulatory guidance limiting the duration of use of topical antibiotics (alone and in fixed-dose combination products) to 11 to 12 weeks.
- Use BPO concomitantly as a leave-on or as a wash.
  - BPO for 5 to 7 days between antibiotic courses may reduce resistant organisms on the skin; however, BPO does not fully eradicate potential for resistant organisms.
- Avoid using antibiotics (either oral or topical) as a monotherapy either for the acute treatment or maintenance therapy.
- Avoid the simultaneous use of oral and topical antibiotics without BPO, particularly if chemically different.

<table>
<thead>
<tr>
<th>Comedonal acne</th>
<th>Mild-to-moderate papulopustular acne</th>
<th>Severe papulopustular/moderate nodular acne</th>
<th>Severe nodular/conglobate acne</th>
</tr>
</thead>
<tbody>
<tr>
<td>High strength of recommendation</td>
<td>-</td>
<td>Adapalene + BPO (f.c.) or BPO + clindamycin (f.c.)</td>
<td>Isotretinoin</td>
</tr>
<tr>
<td>Medium strength of recommendation</td>
<td>Topical retinoid</td>
<td>Azelaic acid or BPO or topical retinoid or systemic antibiotic + adapalene</td>
<td>Systemic antibiotics + adapalene or systemic antibiotics + azelaic acid or systemic antibiotics + azelaic acid or systemic antibiotics + adapalene + BPO (f.c.)</td>
</tr>
<tr>
<td>Low strength of recommendation</td>
<td>Azelaic acid or BPO</td>
<td>Blue light or oral zinc or topical erythromycin + isotretinoin (f.c.) or topical erythromycin + tretinoin (f.c.) or systemic antibiotic + BPO or systemic antibiotic + azelaic acid or systemic antibiotics + azelaic acid or systemic antibiotics + adapalene + BPO (f.c.)</td>
<td>Systemic antibiotics + BPO</td>
</tr>
<tr>
<td>Alternatives for female patients</td>
<td>-</td>
<td>Hormonal antiandrogens + topical treatment or hormonal antiandrogens + systemic antibiotics</td>
<td>Hormonal antiandrogens + systemic antibiotics</td>
</tr>
</tbody>
</table>

European Guidelines to "discourage" bacterial resistance.

Said resistance might reach 80% in 2015!
The phenomenon of antibiotic resistance has led to seek anti-inflammatory therapies that do not develop resistance against pathogens that are not only the cause of acne but also, and especially, of other infectious diseases. The combination of Micronized Silver, Zinc Acetate and Lauric Acid meets these requirements for the antiseptic, anti-inflammatory properties of their components. Particularly, Micronized Silver has an antimicro-
ensures the availability of scarcely toxic products that possess broad spectrum antiseptic properties without developing bacterial resistance. Zinc is a vital element for humans since it is an essential component of more than 300 metalloenzymes and of more than 2,000 transcription factors that are necessary to regulate the metabolism of lipids, proteins and nucleic acids. The mean content in humans is 1.5-2.5 g, and it is especially found in


The zinc content of foods (mg/100 g).

<table>
<thead>
<tr>
<th>Food</th>
<th>Zinc (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlantic Oysters</td>
<td>74.7</td>
</tr>
<tr>
<td>Wheat germ</td>
<td>14.3</td>
</tr>
<tr>
<td>Beef</td>
<td>6.2</td>
</tr>
<tr>
<td>Cocoa powder</td>
<td>5.6</td>
</tr>
<tr>
<td>Cheese</td>
<td>4.0</td>
</tr>
<tr>
<td>Oats</td>
<td>3.4</td>
</tr>
<tr>
<td>Durum wheat</td>
<td>3.4</td>
</tr>
<tr>
<td>Dried peas</td>
<td>3.2</td>
</tr>
<tr>
<td>Lentils</td>
<td>3.1</td>
</tr>
<tr>
<td>Walnuts*</td>
<td>3.1</td>
</tr>
<tr>
<td>Almonds*</td>
<td>3.0</td>
</tr>
<tr>
<td>Black-eyed beans</td>
<td>2.9</td>
</tr>
<tr>
<td>Peanuts</td>
<td>2.9</td>
</tr>
<tr>
<td>Ham</td>
<td>2.8</td>
</tr>
<tr>
<td>Beans</td>
<td>2.8</td>
</tr>
<tr>
<td>Veal</td>
<td>2.8</td>
</tr>
<tr>
<td>Soft wheat</td>
<td>2.7</td>
</tr>
<tr>
<td>Chickpeas</td>
<td>2.7</td>
</tr>
<tr>
<td>Whole-wheat flour</td>
<td>2.4</td>
</tr>
<tr>
<td>Chicken</td>
<td>2.4</td>
</tr>
<tr>
<td>Wholemeal bread</td>
<td>1.8</td>
</tr>
<tr>
<td>Brown rice</td>
<td>1.8</td>
</tr>
<tr>
<td>Rye bread</td>
<td>1.6</td>
</tr>
<tr>
<td>Semi-whole wheat flour</td>
<td>1.5</td>
</tr>
<tr>
<td>2 Eggs, 50 g each</td>
<td>1.0</td>
</tr>
<tr>
<td>Spinach, raw</td>
<td>0.8</td>
</tr>
<tr>
<td>Fish</td>
<td>0.7</td>
</tr>
<tr>
<td>White bread</td>
<td>0.6</td>
</tr>
<tr>
<td>Common pasta, cooked</td>
<td>0.5</td>
</tr>
<tr>
<td>Tomato, ripe</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*(N. Valerio, da Kreuse & Mahan 1984 e *USA Dept. Agr.)*

The anti-inflammatory properties of zinc are the reason for its use in several inflammatory dermatoses, such as acne, rosacea, eczema, ulcers and wounds. In 1974 G. Michaelsson reported the improvement of acneic lesions in a patient presenting acrodermatitis entropathica treated with zinc salts. The mechanism of its efficacy in the treatment of acne has still not been entirely explained. Topical zinc alone or combined with other agents may be effective in the case of acne for its anti-inflammatory action and the capacity to reduce the P. acnes load by inhibiting lipase and free fatty acid levels. Moreover, it facilitates the absorption of the antibiotic when used in combination with it.

Lauric Acid (LA) is a medium chain saturated fatty acid that is made up of 12 carbon atoms, and which is found in dairy products, animal fats and tropical oils, such as coconut oil. The cell membrane is permeable to LA, which forms 1-2% of free fatty acids (FFA) of sebum with a higher antimicrobial action than all other FFAs by exerting an inhibitory effect on the growth of P. acnes, S. aureus and S. epidermidis at a concentration that is 15 times lower than benzoyl peroxide. Lauric acid determines a significant suppression of IL-8 induced by P. acnes and of IL-6 induced by sebocytes.

The combination of LA with other local antimicrobial therapies can increase the capacity to cross the bacterial membrane, thus enhancing the antimicrobial action. Hence, LA is a potential alternative therapeutic option for antibiotic-therapy in the prostate gland, seminal fluid, uveal tract tissue and skin. The recommended daily dose for adults is 11 mg, which can be increased in women during pregnancy and breast-feeding. It circulates in the blood bound to albumin and alpha-2-macroglobulin, and is, especially, excreted in faeces. One third of the world population presents zinc deficiency in South East Asia and in Saharan Africa.

Zinc has antioxidant properties. It reduces UV-induced damages and the incidence of malignant tumours. It is involved in the maintenance of reproductive and immune function, and in the wound repair process. It has anti-androgenic and sebum-suppressive properties by inhibiting 5-alpha-reductase.

![Lauric Acid](image)
Micronized Silver + Zinc Acetate + Lauric Acid + a specific cleansing agent for acneic skin containing Taurates, Silver Citrate and microspheres of Silicon twice a day. Sixteen of these patients presented a family history of acne. A Group B of 20 subjects with slight-moderate acne, 8 males and 12 females, with mean age 16 years, treated with the same topical combination + a non-specific cleansing agent for acneic skin containing acyl-glutamates and mallow twice a day. Sixteen patients presented a family history of acne.

Results

Group A

- First visit
- 1st follow-up visit after 4 weeks (T1)
- 2nd follow-up visit after 8 weeks (T2)
- 3rd follow-up visit after 12 weeks (T3)

The third visit was only attended by 13 patients because 7 of them had achieved "clinical healing" already at the second follow-up visit. None of the patients presented side-effects, such as dry skin, desquamation, itching and rash, during all the follow-up visits. All products were highly tolerated.
GROUP A

Highly significant reduction in the number of lesions, inflammatory (especially).

T3* visit performed only on 13 patients.

GROUP B

- The IGA Score of patients diminishes significantly at the end of treatment.
- The assessment of the IGA Score of 20 patients at T0, T3 revealed a progressive improvement in the clinical condition with a reduction in the score and a result of mild/absent.

The third visit was only attended by 10 patients because 10 of them had achieved “clinical healing” already at the second follow-up visit.
**Clinical pictures**

**Conclusions**

The combination of Micronized Silver + Zinc Acetate + Lauric Acid is effective in reducing acneic lesions, both inflammatory and non-inflammatory, in both treated groups.

The statistically significant reduction is more enhanced for inflammatory lesions and, however slightly, said reduction is more pronounced in the group combined with the specific cleansing agent.
for acne skin (Group A). Sebum reduction is not highly significant in any of the two groups. The IGA score is significantly reduced in both groups from the initial visit to the last follow-up visit. Treatment tolerability was excellent. The combination of Micronized Silver + Zinc Acetate + Lauric Acid might also be used in combination with a topical keratolytic/retinoid agent to boost its efficacy in moderate acne forms with an important comedo component. We can conclude that, considering its anti-inflammatory efficacy and excellent tolerability, the combination of Micronized Silver + Zinc Acetate + Lauric Acid might be an effective therapeutic option for slight-moderate acne vulgaris presenting an inflammatory component, without the onset of bacterial resistance!

References

Role of cleaners in the management of acne: results of an Italian survey in 786 patients

**Summary**

Modern therapy of acne is based also on “complementary” products, such as moisturizers, cleansers and sunscreens. All these products have acquired, in the last years, a great importance: it is crucial the role of moisturizers in the management of irritant contact dermatitis caused by retinoids. However, while there is a rich literature on moisturizers, the same cannot be stated for cleansers, for which a few studies have been published, and never in Italy. For these reasons, we decided to carry out an epidemiological study on the knowledge, beliefs and perceptions of acne patients regarding cleansers.

The survey has been carried out in Italy in 2013-2014. A group of patients with a diagnosis of acne, made by their dermatologist, completed a questionnaire, given them by their dermatologist, which included the following ten questions:

1. “Do you use a specific cleanser for your acne?”
2. “Who/what suggested you to use this cleanser?”
3. “Where did you buy this cleanser?”
4. “Are you satisfied about this cleanser?”
5. “How many times a day do you use this cleanser?”
6. “How long is each washing?”
7. “Do you think that a specific cleanser for acne has a therapeutic role?”
8. “Do you prefer liquid or “solid” cleansers?”
9. “Do you prefer scented or fragrance-free cleansers?”
10. “Do you prefer foamy or not foamy cleansers?”

Results

One hundred eighteen dermatologists and 786 evaluable acne patients [248 males (31.6%) and 538 females (68.4%), with an age ranging from 11 to 48 years (median: 23.9 years)], attended the survey.

Acne was classified by dermatologists as comedonal-papular-pustular in 383 patients (48.7%), predominantly comedonal in 189 (24%), predominantly papular in 112 (14.2%), predominantly pustular in 59 (7.5%), predominantly nodular-cystic in 41 (5.2%) and not specified in 2 (0.3%) (Table 1).

Table 1. Clinical varieties of acne.

<table>
<thead>
<tr>
<th>Type of acne</th>
<th>Males N. of pts</th>
<th>%</th>
<th>Females N. of pts</th>
<th>%</th>
<th>Total N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedonal-papular-pustular</td>
<td>123</td>
<td>49.6%</td>
<td>260</td>
<td>48.3%</td>
<td>383</td>
<td>48.7%</td>
</tr>
<tr>
<td>Comedonal</td>
<td>52</td>
<td>21%</td>
<td>137</td>
<td>25.5%</td>
<td>189</td>
<td>24%</td>
</tr>
<tr>
<td>Papular</td>
<td>26</td>
<td>10.5%</td>
<td>86</td>
<td>16%</td>
<td>112</td>
<td>14.2%</td>
</tr>
<tr>
<td>Pustular</td>
<td>25</td>
<td>10.1%</td>
<td>34</td>
<td>6.3%</td>
<td>59</td>
<td>7.5%</td>
</tr>
<tr>
<td>Nodular-cystic</td>
<td>21</td>
<td>8.4%</td>
<td>20</td>
<td>3.7%</td>
<td>41</td>
<td>5.2%</td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
<td>0.4%</td>
<td>1</td>
<td>0.2%</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>Total</td>
<td>248</td>
<td>100%</td>
<td>538</td>
<td>100%</td>
<td>786</td>
<td>100%</td>
</tr>
</tbody>
</table>

Acne was judged as mild in 286 patients (36.4%), moderate in 415 (52.8%), severe in 70 (8.9%) and not specified in 15 patients (1.9%) (Table 2).

At the beginning of the survey, 731 out of 786 patients (93%) were in treatment with topical products or drugs: 282 patients were in treatment with antibiotics (38.6%), 260 with retinoids (35.6%), 253 with antiseptics (34.6%), 127 with salicylic acid (17.4%), 75 with nicotinamide (10.3%), 62 with azelaic acid (8.5%) and 38 with other products (glycolic acid, pyruvic acid, ...) (5.2%) (Table 3).

Table 2. Severity of acne.

<table>
<thead>
<tr>
<th>Severity of acne</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>286</td>
<td>36.4%</td>
</tr>
<tr>
<td>Moderate</td>
<td>415</td>
<td>52.8%</td>
</tr>
<tr>
<td>Severe</td>
<td>70</td>
<td>8.9%</td>
</tr>
<tr>
<td>Not specified</td>
<td>15</td>
<td>1.9%</td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 3. Topical therapy at the beginning of the survey.

<table>
<thead>
<tr>
<th>Severity of acne</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>282</td>
<td>38.6%</td>
</tr>
<tr>
<td>Retinoids</td>
<td>260</td>
<td>35.6%</td>
</tr>
<tr>
<td>Antiseptics</td>
<td>253</td>
<td>34.6%</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>127</td>
<td>17.4%</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>75</td>
<td>10.3%</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>62</td>
<td>8.5%</td>
</tr>
<tr>
<td>Others *</td>
<td>38</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

* Glycolic acid, pyruvic acid, ...
Table 4.
Oral therapy at the beginning of the survey.

<table>
<thead>
<tr>
<th>Oral therapy</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>264</td>
<td>65.5%</td>
</tr>
<tr>
<td>Hormones</td>
<td>69</td>
<td>17.1%</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>61</td>
<td>15.1%</td>
</tr>
<tr>
<td>Others *</td>
<td>32</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

* Zinc, lactoferin, biotin, inositol...

Table 5.
Do you use a specific cleanser for your acne?

<table>
<thead>
<tr>
<th>Specific cleanser</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>543</td>
<td>69.1%</td>
</tr>
<tr>
<td>No</td>
<td>243</td>
<td>30.9%</td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 6.
Who/what suggested you to use this cleanser?

<table>
<thead>
<tr>
<th>Suggested by</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologist</td>
<td>310</td>
<td>57.1%</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>87</td>
<td>16%</td>
</tr>
<tr>
<td>Friends</td>
<td>24</td>
<td>4.4%</td>
</tr>
<tr>
<td>Beautician</td>
<td>23</td>
<td>4.2%</td>
</tr>
<tr>
<td>Journals, magazines, television</td>
<td>19</td>
<td>3.5%</td>
</tr>
<tr>
<td>General practitioner</td>
<td>14</td>
<td>2.6%</td>
</tr>
<tr>
<td>Member of the family</td>
<td>13</td>
<td>2.4%</td>
</tr>
<tr>
<td>Internet</td>
<td>13</td>
<td>2.4%</td>
</tr>
<tr>
<td>Others/not specified</td>
<td>40</td>
<td>7.4%</td>
</tr>
<tr>
<td>Total</td>
<td>543</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 7.
Do you use a specific cleanser for your acne?

<table>
<thead>
<tr>
<th>Purchased at:</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy</td>
<td>421</td>
<td>77.5%</td>
</tr>
<tr>
<td>Supermarket</td>
<td>47</td>
<td>8.7%</td>
</tr>
<tr>
<td>Perfumery</td>
<td>22</td>
<td>4.1%</td>
</tr>
<tr>
<td>Internet</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Others/not specified</td>
<td>50</td>
<td>9.1%</td>
</tr>
<tr>
<td>Total</td>
<td>543</td>
<td>100%</td>
</tr>
</tbody>
</table>

The 2nd question was: “Who/what suggested you to use this cleanser?” The answers were: the dermatologist (310 patients = 57.1%), the pharmacist (87 patients = 16%), a friend (24 patients = 4.4%), the beautician (23 patients = 4.2%), journals/magazines/television (19 patients = 3.5%), general practitioner (14 patients = 2.6%), a member of my family (13 patients = 2.4%), internet (13 patients = 2.4%), others or not specified (40 patients = 7.4%) (Table 6).

The 3rd question was: “Where did you buy this cleanser?” The answers were: at pharmacy (421 patients = 77.5%), at supermarket (47 patients = 8.7%), at perfumery (22 patients = 4.1%), by internet (3 patients = 0.6%), others or not specified (50 patients = 9.3%) (Table 7).

The 4th question was: “Are you satisfied about this cleanser?”: 338 patients answered “yes” (62.2%), 200 patients answered “no” (36.8%) and 5 patients answered “I do not know” (0.9%) (Table 8).

The 5th question was: “How many times a day do you use this cleanser?”: 136 patients answered “once a day” (25%), 361 patients answered “twice a day” (66.5%), 41 patients answered “thrice a day” (7.6%), one patient answered “more than thrice a day” (0.2%) and 4 patients did not specify (0.7%) (Table 9).

The 6th question was: “How long is each washing?”: 262 patients answered “less than one minute” (48.3%), 255 patients answered “2 to 3
Table 10. How long is each washing?

<table>
<thead>
<tr>
<th>Length of washing</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 minute</td>
<td>262</td>
<td>48.3%</td>
</tr>
<tr>
<td>2 to 3 minutes</td>
<td>255</td>
<td>47%</td>
</tr>
<tr>
<td>More than 3 minutes</td>
<td>21</td>
<td>3.9%</td>
</tr>
<tr>
<td>Not specified</td>
<td>5</td>
<td>0.9%</td>
</tr>
<tr>
<td>Total</td>
<td>543</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 11. Do you think that a specific cleanser for acne has a therapeutical role?

<table>
<thead>
<tr>
<th>Therapeutical role of cleansers</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>524</td>
<td>66.7%</td>
</tr>
<tr>
<td>I do not know</td>
<td>192</td>
<td>24.5%</td>
</tr>
<tr>
<td>No</td>
<td>70</td>
<td>8.9%</td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 12. Do you prefer liquid or “solid” cleansers?

<table>
<thead>
<tr>
<th>Liquid/solid cleansers</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid</td>
<td>615</td>
<td>78.2%</td>
</tr>
<tr>
<td>I do not know</td>
<td>152</td>
<td>19.3%</td>
</tr>
<tr>
<td>Solid</td>
<td>19</td>
<td>2.4%</td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 13. Do you prefer scented or fragrance-free cleansers?

<table>
<thead>
<tr>
<th>Perfume of cleansers</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scented</td>
<td>327</td>
<td>41.6%</td>
</tr>
<tr>
<td>I do not know</td>
<td>257</td>
<td>32.7%</td>
</tr>
<tr>
<td>Fragrance-free</td>
<td>202</td>
<td>25.7%</td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 14. Do you prefer foamy or not foamy cleansers?

<table>
<thead>
<tr>
<th>Foamy/not foamy cleaners</th>
<th>N. of pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foamy</td>
<td>409</td>
<td>52%</td>
</tr>
<tr>
<td>Not important</td>
<td>239</td>
<td>30.4%</td>
</tr>
<tr>
<td>Not foamy</td>
<td>138</td>
<td>17.6%</td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td>100%</td>
</tr>
</tbody>
</table>

minutes” (47%), 21 patients answered “more than three minutes” (3.9%) and 5 patients did not specify (0.9%) (Table 10).

The 7th question was: “Do you think that a specific cleanser for acne has a therapeutical role?”: 524 patients answered “yes” (66.7%), 192 patients answered “I do not know” (24.5%) and 70 patients answered “no” (8.9%) (Table 11).

The 8th question was: “Do you prefer liquid or “solid” cleansers?”: 615 patients answered “liquid” (78.2%), 152 patients answered “I do not know” (19.3%) and 19 patients answered “solid” (2.4%) (Table 12).

The 9th question was: “Do you prefer scented or fragrance-free cleansers?”: 327 patients answered “scented” (41.6%), 257 patients answered “I do not know” (32.7%) and 202 patients answered “fragrance-free” (25.7%) (Table 13).

The last question was: “Do you prefer foamy or not foamy cleansers?”: 409 patients answered “foamy” (52%), 239 patients answered “I do not know” (30.4%) and 138 patients answered “not foamy” (17.6%) (Table 14).

Discussion

The role of cleansers in the management of acne was studied since 1970’s. In 1995, Korting et al. published the first clinical study on the efficacy of an acid syndet. In this randomized, open trial, the syndet was compared to an alkaline soap in 120 adolescents and young adults with inflammatory acne of the face. Both cleansers were applied for 1 minute in the morning and in the evening for three months. In the group which used the soap the mean number of inflammatory lesions increased, while it decreased in the group which used the syndet. Symptoms and/or signs of irritation were observed in 40.4% of patients belonging to the soap group and in 1.8% to the syndet group.

In 1996, Solomon and Shalita published the first review on the effects of cleansers in acne. Since then,
some articles were published on this topic demonstrating some clinical efficacy of cleansers in acne.\textsuperscript{18-22}

Choi et al.\textsuperscript{18} studied the effect of frequency of face washing. The authors designed a single-blind, randomized, controlled clinical trial in males with mild to moderate acne. Patients washed their faces twice daily for two weeks with a standard cleanser before being randomized to one of three study arms, in which washing was to be done once, twice or four times a day for six weeks. At the end of the study, no statistically significant differences were noted between groups. However, significant improvement in both open comedones and noninflammatory lesions were observed in the group washing twice a day. Worsening of acne was observed in the group washing once a day, with significant increase in erythema, papules and inflammatory lesions. The authors concluded that slight support exists, in term of efficacy, for the recommendation to wash the face twice daily with a cleanser.

In a recent review of the literature, in which all randomized and controlled/uncontrolled clinical trials were considered, the authors stated that: a) most cosmetic products for acne can enhance the clinical outcome; b) cleansers should be prescribed to all acne patients and c) cleansers containing benzoyl peroxide or azelaic/salicylic acid/triclosan show the best efficacy profile.\textsuperscript{23} Very little is known about the beliefs and perceptions of young patients with acne on cleansers. In a Canadian study published in 2001,\textsuperscript{24} non-prescription products used most frequently by acne patients were cleansers, acne pads and lotions. Poor skin hygiene was considered as implicated in acne pathogenesis. Information on acne was obtained primarily from general practitioners, mass media, friends and family, but was largely believed to be inadequate.\textsuperscript{24} A voluntary self-completed questionnaire was used to collect data from acne patients visiting a hospital in Saudi Arabia.\textsuperscript{25} One hundred-thirty patients completed the questionnaires. Doctors were the most common source of information for patients. Most patients believe that dirt was the major cause of acne. Most patients (46.1\%) had used skin cleansers before seeking medical advice. In 539 randomly selected students aged 11-19 years in a secondary school in Nigeria, cleansing agents were the most commonly used treatments.\textsuperscript{26}

Finally, Drèno et al.\textsuperscript{27} published in 2010 the results of a study in which they used a simple, validated questionnaire (the Elaboration d’un outil d’évaluation de l’observance des traitements médicamenteux, ECORB) to assess the risk of poor adherence in a large worldwide cohort of acne patients (n = 3,339) from America, Europe and Asia. The authors observed that a factor that had a positive effect on adherence was the use of moisturizers and cleansers. To our knowledge, our study is the largest published survey on the knowledge, beliefs and perceptions of acne patients regarding the use of cleansers in the management of the disease.

The results of this survey may be summarized as follows:

a) approximately 70\% of patients uses a specific anti-acne cleanser;

b) this cleanser is suggested in more than 57\% of cases by a dermatologist, followed by a pharmacist (16\% of cases);

c) the patients buy this cleanser at the pharmacy (more than 77\% of cases);

d) more than 62\% of patients is satisfied about this cleanser;

e) more than 66\% of patients uses the cleanser twice daily; ¼ of patients uses the cleanser once daily;

f) the length of washing is less than one minute in more than 48\% of patients, and 2 to 3 minutes in 47\% of patients;

g) more than 66\% of patients believes that the cleanser has a therapeutical role;

h) more than 78\% of patients prefers a liquid cleanser;

i) more than 41\% of patients prefers a scented cleanser, whereas approximately 25\% prefers as fragrance-free cleanser;

j) more than 50\% of patients prefers a foamy cleanser (not foamy in more than 17\% of patients).

These results cannot be compared with other studies because of the lack of studies about this topic. These results suggest that a sample of Italian acne patients consider cleansers as an important adjuvant treatment in acne.
References

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Hyaluronan: a potent skin matrix macromolecule for wound healing

SUMMARY

The important biological role of hyaluronan in the correct function of skin cells and in the regenerative tissue repair highlighted this molecule as a target of many studies for the investigation of therapeutic creams for the local treatment of skin disorders, such as chronic wounds and burns but also in aesthetic medicine procedures. In this review, we provide information for the principal functions and factors that influence the metabolism of hyaluronan. Because of the simplicity of the structure of this macromolecule, the different molecular weights have a biological relevance and the hyaluronan size determines its role in different conditions as in inflammation and cancer. Thus, the last part of this review is focused mainly on the role of low molecular weight hyaluronan in wound healing, concerning the binding to toll-like receptors 2 and 4 and the biological pathways triggered by this interaction that implies the stimulation of skin innate immunity.

Key words: Hyaluronan; Wound healing; Tissue injury; Inflammation.

The extracellular matrix of the skin

Human skin is a multiple layer tissue, composed of various types of cells immersed within a complex matrix of macromolecules, such as collagen and hyaluronan (HA). Skin layers are divided in: epidermis, dermis and hypodermis. Epidermis is mainly composed of keratinocytes in various stages of differentiation and with few melanocytes. Keratinocytes in stratum basale are highly differentiated and belong to the epidermal stem cells that are highly important for the regeneration of the skin in cutaneous injuries. During migration towards the upper epidermal layers, keratinocytes change their shape, loose their proliferative potential and produce more keratin, which is finally employed in the assembly of the most outer layer of the skin, called horny layer. The epidermis has no blood vessels, relying nutrients on the dermis. In the last decades, it was found that HA is present at very high concentrations in the narrow extracellular space between the stratified keratinocytes of epidermis and has a local turnover time of less than 1 day 1-4. Epidermis and dermis are separated by a thin layer of basement membrane, composed of lamina lucida and densa as well as anchoring filaments and dermal collagen fibrils. The dermis is a dense connective tissue and contains elastic fibres, collagen and reticular fibres. In dermis, collagen constitutes the 70% of the extracellular matrix (ECM) proteins and of this the 85% is type I collagen and the 15% is type III collagen. A ground substance of dermis ECM contains HA, chondroitin sulphate, proteoglycans and glycoproteins. In humans, HA is the most abundant GAG in the ECM. Specifically, the skin contains about 50% of the whole body HA content, i.e. for an adult of 70 kg, the skin has about about 15 g of HA. The hypodermis consists primarily of loose connective tissue and adipose tissue. Skin morphology and composition change during ageing, inflammation and from external conditions, such as burn, wounds and infections. For instance, dermis during ageing tends to lose the organization of collagen fibres, whereas basement membrane and epidermis become thinner 5, 6. In the last years, research has been focused on the
involvement of HA in the physiological and pathological conditions of the skin as well as in the synthesis of biomaterials. In this report, we review scientific results regarding the role of HA in inflammation and the clinical role of HA in wound healing and some dermatologic disorders.

**Hyaluronan: functions... and turnover in skin**

The HA is one of the major constituents of the ECM of skin and is mainly localized in the dermis, even though recent studies demonstrated a notated amount of HA around the keratinocytes of epidermis with great significance in the metabolism and biological functions. Structurally, HA is a linear polysaccharide of high molecular weight and is composed of the repeating disaccharide containing glucuronic acid and N-acetylglucosamine. The HA belongs to the family of glycosaminoglycans (GAG) but contrarily to the other GAGs, it is neither sulphated nor linked to a protein core. Because of the hydrophilic property, HA is very important for the hydration of the skin and the right organization of ECM macromolecules, such as collagen and proteoglycans. Additionally, HA promotes signaling pathways that regulate cell functions through interaction with cell surface receptors, such as CD44, RHAMM, LYVE-1 and toll-like receptor-4 (TLR4). Different molecular weights of HA have a different role in biological processes. Indeed, high molecular weight HA (HMW HA, > 1000 kDa) facilitates cell migration and differentiation and is anti-angiogenic, anti-inflammatory and immunosuppressive whereas low molecular weight HA (LMW HA, 10-500 kDa) facilitates cell proliferation and is highly angiogenic and pro-inflammatory. A recent study demonstrated that topical application of HA, with molecular weight of 27 kDa, in aged mouse skin promotes keratinocyte proliferation and increases skin thickness, whereas HMW HA restores keratinocyte differentiation and improves permeability barrier function in aged epidermis.

The molecular weight of HA is controlled by enzymes that synthesize or degrade this molecule. In human dermal fibroblasts, HA is synthesized by three distinct HA synthases (HAS1, HAS2 and HAS3) which are localized on the cell membrane. Dermal fibroblasts and epidermal keratinocytes mainly express HAS2 which synthesizes a high molecular weight HA. Synthesis of HAS2 enzyme is affected by various growth and other factors, whereas its activity was found to be regulated by post-translational modifications. Specifically, human HAS2 enzyme is active when it is monophosphorylated. Additionally, it was demonstrated in in vitro experiments that stimulation of phosphorylation of HAS2 in human skin fibroblasts was associated with an increased HA secreted amount. However, this phenomenon was inverted when an O-linked β-N-acetylglucosaminylolation (O-GlcNAcylation) of HAS2 was stimulated, showing a competition between phosphorylation and O-GlcNAcylation. Recently, it was shown that HAS2 has an important role in cellular functions, such as epithelial-mesenchymal transition (EMT), migration and apoptosis. Experiments on skin fibroblasts obtained from Has1/3 null mice showed that these cells present an induced Has2 gene expression accompanied by an increased resistance to stress-induced apoptosis, provoked for example from UV exposure and wound healing. Moreover, keratinocytes from keloid scars showed an increased gene expression of HAS2, but not of HAS1 and HAS3, as well as an increased migration of these cells respect to normal keratinocytes. These results render HAS2 an important membrane enzyme not only for the HA synthesis and homeostasis of the connective tissue but also for the right function and protection of the skin cells. Degradation of HA to fragments is performed by the family of cystolic enzymes hyaluronidases (HYALs). Human dermal fibroblasts from adults and fetuses express two HYALs, known with the abbreviations HYAL-1 and HYAL-2. These two enzymes that are found in most of the somatic cells are both encoded from the chromosome 3p21.3. HYAL-2 cleaves HMW HA polymers to intermediate size fragments of approximately 20 kDa, whereas further degradation to LMW oligosaccharides is occurred by HYAL-1. HYAL-1 was found to have an acidic pH optimum and had properties that suggested it was membrane associated. HYAL2 was...
found to localize to the lysosome and to have an acidic pH optimum. An abnormal increased degradation of HA in the skin is associated to an endogenous signal of injury and inflammation.

**Role of hyaluronan in wound healing and inflammation**

The HA plays a key role in both fibrotic and regenerative tissue repair. It is generally considered that different molecular weights of HA have different effect in wound healing and inflammation. For instance, accumulation of HMW HA is typical of regenerative repair, which is associated with minimal inflammation and fibrosis. On the other hand, HA fragments are typically associated with postnatal and adult wounds, which heal in the presence of inflammation and transient fibrosis.

In a recent work, it was demonstrated that the 6-8mer oligosaccharides significantly stimulated scratch wound repair. Specifically, the 6mer HA that required RHAMM and CD44 expression promoted wound closure, accumulation of wound M1 and M2 macrophages and the M2 cytokine TGF β1, but did not increase myofibroblast differentiation. In the same study, it was shown that the 40mer HA fragment inhibited wound closure, increased the number of wound macrophages but had no effect on TGF β1 accumulation or subsequent fibrosis.

The 200kDa HA fraction has been proven to be the most active one in order to enhance the wound healing process. In form of cream, LMW HA accelerates the re-epithelization of wounds, thanks to its proliferative and migration promoting effects on basal keratinocytes. Moreover, this HA fraction enhances fibroblast proliferation and migration and plays a protective role of the wound provisional matrix towards the free radicals, generated either during the inflammatory phase or by deep UV radiation penetration into the dermis. Additionally to HA, TLR2 and TLR4 play important roles in non-infectious inflammation and tissue repair and regeneration. The HA oligosaccharides, which in tissue injury are considered endogenous danger signals and activate the innate immune defence, are linked to TLR2 and TLR4 providing signals that initiate inflammatory responses, maintain epithelial cell integrity, and promote recovery from acute injury. TGF-β1, which is a growth factor secreted by macrophages stimulated by HA, is also known to enhance wound repair. A recent study on knock-out mice for TLR2 and/or TLR4 demonstrated that TLR4, rather than TLR2, regulates wound healing through TGF-β expression. Indeed, skin wound healing was impaired in TLR2−/−, TLR4−/−, and TLR2/4−/− mice compared to wild-type mice, with decreased macrophage infiltration and reduced TGF-β mRNA expression.

During skin lesions, keratinocytes of epidermis secrete soluble factors with antibacterial factors, among them the peptides β-defensins. The release of β-defensin-2 (DEFB2) by skin keratinocytes is induced by LMW HA during skin lesion and inflammation through stimulation of TLR2 and TLR4. The TLR signalling pathway may activate a variety of transcription factors, such as c-fos and activator protein-1 (AP-1), that lead to activation of different genes and the release of cytokines. Gariboldi et al. demonstrated that c-fos is linked to DEFB2 promoter in keratinocytes, after treatment of these cells with HA oligosaccharides. Thus, low LMW HA is linked to TLR2 and TLR4 that activate the signalling pathway of AP-1 family, inducing the DEFB2 expression and secretion. These observations suggest that HA oligosaccharides may be used for the topical application on the injured skin as a stimulator of cutaneous antibacterial activity (Figure 1).

Interestingly, HA oligomers, i.e. generated from the interaction with ROS or by PMN cells during the inflammatory phase of the wound healing process, exerts a consistent pro-angiogenic effect, stimulating the proliferation of endothelial cells through a receptor-mediated mechanism where both RHAMM and ICAM1 receptors are involved. As a consequence of neo-angiogenesis, more granulation tissue formation is produced, which is a necessary step for the initiation of the healing process.

Studies on tissue engineering involve the use of HA in the skin repair especially in the more severe wound situations, such as in burn and diabetic wounds. Because of the simple structure of
HA, its use in biomaterials includes various molecular weights or even modifications of the molecule, such as the sulphated HA\(^\text{41, 42}\).

**Clinical use of HA... on wound healing**

The remarkable properties of HA have led to its use in a number of clinical applications. Exogenous applied HA was shown to provide a beneficial effect in wound healing and on topical intact skin applications in case of certain dermatologic disorders. When detailing HA healing properties, it is always important to state the precise MW range of the HA preparation according to which a certain biological or clinical effect is ascribed. In a randomized controlled multicenter clinical trial, the efficacy of LMW HA was evaluated in 50 patients with venous ulcers in comparison with Dextranomer (in addition to compressive dressing which was provided to both groups). A faster and greater reduction in the ulcer dimensions in the LMW HA-treated group was found. In addition only LMW HA was able to significantly decrease the edema formation\(^{43}\).

Costagliola and Agosti\(^{44}\) reported that in a randomized-controlled double blind multicenter study, a LMW (200kDa) HA cream containing 1% silver sulfadiazine (SSD) was compared to 1% SSD preparation in the treatment of second degree burns. In this study a number of 111 patients were enrolled and it was found that the combination of HA-SSD caused a significant more rapid re-epithelialization of burns, with a shorter mean healing time of 4.5 days, than SSD alone (\(p = 0.0073\)). This result can be ascribed to the enhancement of keratinocytes migration by the 200 kDa fraction of HA.
A concentration of 0.2% LMW HA has been also used in combination with a debriding enzyme (collagenase from Vibrio alginolyticus), as a topically applied ointment. In this case, the rationale of the combined product is to accomplish a more effective wound bed preparation, thanks to the enzymatic degradation of fibrin and slough/necrotic tissue, along with an enhanced re-epithelialization due to the LMW HA fraction. Onesti et al. reported that in an open, prospective observational monocentric study on chronic leg ulcers, 32 patients out of 40 achieved a relevant reduction of the ulcer size with an improvement of the wound bed and a reduction of fibrin and exudates. Of these, 14 patients presented a complete healing while 36 patients reported a remarkable pain reduction, with 16 patients referred no pain at all at dressing changes. These findings have been confirmed by Gravante et al. in a multicenter observational study on venous ulcers. A number of 100 patients had been enrolled and treated with the previous described ointment in 4 centres. All patients achieved complete debridement of the necrotic area and a significant reduction of the total ulcer area by day 20, while other parameters improved significantly over time.

On intact skin, LMW HA has also been proven effective in order to decrease inflammation and preventing further damage following an aggressive treatment, such as (dermal) radiotherapy. In fact, a randomized, double-blind, placebo-controlled study using LMW HA of 200kDa (0.2% cream) was carried out in 134 patients to investigate the prophylactic use of LMW HA after radiotherapy treatment. Twice daily applications of the HA cream caused only a slight delay on the onset of acute skin reactions but significantly reduced their intensity compared to the placebo cream treatment. Additionally the healing process of the HA-based cream group appeared accelerated.

The above mentioned studies have been conducted on lesions or impaired skin, therefore migration of 200kDa HA into the dermis was not an issue. On the contrary, the epidermal barrier, (more specifically the stratum corneum), avoids HMWHA to penetrate into the dermis, while small HA oligomers (MW< 40kDa) can pass across the epi-dermis reaching the dermal compartment. In the same work, it was demonstrated that 400-200 kDa HA fraction was able to reverse skin atrophy in three aged patients by a CD44 dependent mechanism. Topical application of the 400-200 kDa HA cream was found to cause significant skin thickening in patients with age- or corticosteroid-related skin atrophy. Interestingly, the same topical HA application in healthy subjects, either young adults or aged ones, did not cause keratinocytes hyperproliferation. Therefore, it seems that LMW HA acts like maintaining the epidermal tissue homeostasis, more than providing a direct proliferative response. In in-vivo experiments, highly purified fractions, more restricted in the molecular weight range (< 50 kDa, 100-400 kDa, > 400 kDa), clarified that while the higher MW fraction did not overcome the epidermal barrier, the lower ones did, but only the 100-400 kDa fraction was able to stimulate mouse keratinocyte proliferation in vitro and induce a marked epidermal hyperplasia in vivo.

More recently, a LMW HA (200kDa) preparation has been reported to exert a protective and lenitive effect on rosacea and facial seborrheic dermatitis. In a prospective, non-blinded observational monocentric study a 0.2% LMW HA cream was tested as topical skin application in order to normalizing the cutaneous inflammatory response. 15 adult patients with mild to moderate facial rosacea were enrolled and instructed to apply the HA cream twice daily for 4 weeks, in association with a cleansing product. Then, patients had to discontinue the HA cream application but continued the cleansing regime for an additional 4 weeks. Control visits were scheduled at baseline, week 2, 4 and 8. Outcome measures included papules, pustules, erythema, edema, telangiectasia, burning/stinging and dryness, according to a 5-point scale and through visual grading assessment. The mean reductions in papules, erythema, burning or stinging and dryness at week 4 were 47%, 51.7%, 65% and 78.8% respectively. Erythema was the only parameter to demonstrate continued improvement with a mean reduction of 59% at week 8 while the remaining parameters showed a moderate increase but never reached the initial values, notwithstanding the suspension of the HA treatment. Similar results were
reported on facial seborrheic dermatitis with the same LMW HA cream preparation. It has been postulated that the anti-inflammatory and lenitive effect exerted by the LMW HA preparation could be attributed to the production of DEFB2 by keratinocytes. In fact, when applied topically to the skin, LMW HA may be a potent inducer of DEFB2 in a concentration-dependent manner. The stimulation of skin innate immunity by LMW HA could be a potent mechanism by which 200kDa HA 0.2% cream exerts its beneficial effects in reducing the signs and symptoms of these skin disorders.

Conclusions

Hyaluronan is a major structural and functional component of the cutaneous ECM and fulfills a plenty of functions under physiological and pathological conditions. These different, tremendously varying functional effects of HA in cells and tissues result from different molecular sizes and structures. Due to its physicochemical and dynamic molecular properties, HA can very quickly fill tissue gaps and thus preserve mechanic tissue characteristics beside its biochemical aspects. From the clinical application of HA as a filler or scaffold material, we learn that HA provides a favourable milieu for regeneration by interacting with receptors, signalling molecules and cells.

However, a better understanding of the impact of HA structure, HA polymer size, associated proteins and attached cells will be essential for the rational use of HA either in wound healing, dermatologic diseases or in aesthetic medicine.

References


Programma Preliminare

Acne and Rosacea Days
an International Meeting

MILAN, 6th-7th November 2015

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