Digital image analysis versus clinical assessment of wound epithelialization: A validation study

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\textbf{A B S T R A C T}

To evaluate the progress in wound healing, wound assessment is mandatory. Epithelialization is traditionally assessed subjectively by the clinician. In a previous study, subjective assessment of epithelialization was shown to be reliable. In this study, reliability of epithelialization measured by digital image analysis was investigated and then, we validated the subjective evaluation by comparing this assessment to measurements with digital image analysis. Clinicians assessed epithelialization in 50 burn wounds that were treated with a split skin graft. Epithelialization of these wounds was also measured by three observers using digital image analysis. Reliability of digital image analysis was tested using the intraclass correlation (IC). To test validity, subjective clinical assessment was correlated with digital image analysis (IC). The results showed that interobserver reliability of epithelialization measured by digital image analysis was good (IC coefficient 0.74). Subjective clinical assessment of epithelialization showed a strong correlation with digital image analysis (IC coefficient 0.80). In conclusion, subjective clinical evaluation of wound epithelialization is as good as an objective measure, in this study digital image analysis. Since digital image analysis is more time-consuming, we recommend the use of the subjective evaluation for daily practice.

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\section{Introduction}

Implementation of evidence-based medicine requires valid and reliable tools for assessment of different wound healing parameters. It not only allows clinicians to follow progression of wound healing in a patient; wound assessment is also necessary to evaluate the effectiveness of a specific treatment, especially in clinical trials. In the majority of the reported studies on wound healing, a subjective wound assessment is used, usually performed by one or more clinicians. Also other subjective methods have been described to estimate wound healing, such as qualitative index scores and scales [1–6]. However, quantitative and objective measurements would be preferable when comparing the effects of different wound treatments. Therefore, methods such as ruler-based measurements [7,8], tracings [9,10], and more modern technologies have been developed, e.g.computerized planimetry [11,12], digital image analysis [13], three-dimensional laser [14], optical coherence tomography [15], and light imaging [16].

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A relevant parameter for the evaluation of wound healing, especially in wounds treated with a meshed split-skin graft, is the rate of epithelialization. Although much research has been performed on other aspects of the wound, e.g. wound size, there is a paucity of research on the assessment of epithelialization. Some reports describe the measurement of epithelialization by means of photoplanimetry [17], optical coherence tomography [15], or measuring water evaporation [18], however, these techniques were not evaluated sufficiently on the required clinical properties related to reliability, validity and feasibility. Epithelialization has also been evaluated histologically by means of a biopsy [17,19–21], however, this requires an invasive action and cause pain, infection, and scarring. Objective tools which are feasible, appear to be scarce. We are searching for methods to determine the true value of epithelialization as good as possible. The most important and optimal evaluation of epithelialization still seems to be the clinician’s subjective assessment.

In a previous study, we investigated the reliability of subjective assessment [22]. The intra- and interobserver reliability of subjective assessment of epithelialization was shown to be good when performed by an experienced observer [22]. However, the validity of the subjective clinical assessment is not known, in other words: do the measurements of the experienced observer represent the true rate of epithelialization? In this study, we investigated the validity of the subjective clinical assessment of epithelialization. In order to do this, the evaluation of epithelialization performed by an experienced clinician was compared with epithelialization measured by computerized image analysis, i.e. digital image analysis. Preceding the investigation of the validity of the subjective assessment, the interobserver reliability of digital image analysis was tested, as this was not performed previously for this parameter.

2. Methods

2.1. Study design

The wounds assessed in this study were originating from consecutive burn patients treated in an ongoing multicenter randomized controlled trial (RCT). This trial, performed in the three Dutch Burn Centers, investigates dermal substitution in combination with topical negative pressure in the treatment of acute burns that require skin grafting. The study protocol was approved by the medical ethics committee (M07-035) and registered at Clinical Trials (ID NCT00548314). Peri-operatively, patients (with informed consent) were allocated to the following four treatment groups: (1) dermal substitute in combination with a split-skin graft (SSG) and topical negative pressure; (2) dermal substitute in combination with a SSG; (3) SSG and topical negative pressure; (4) SSG alone. All skin grafts were expanded with a 1:1.5 ratio. Four to seven days after skin transplantation, each patient underwent a visual assessment by the treating clinician. Due to the multicenter setting, this bedside assessment was performed by different experienced clinicians. The wound parameters percentage of epithelialization, graft take and signs of infection were documented. To determine the percentage of wound epithelialization, the clinician first assessed the true expansion of the applied skin graft. Accordingly, in each quadrant of the wound, the graft take and the interstices of the graft were evaluated on vitality and wound healing (epithelialization), which led to a total percentage epithelialization of the entire wound. In addition, a digital photograph of the wound was taken. Photographs were obtained with commercially available digital cameras and were judged to be of high quality, i.e. in focus, showing the relevant wound area, perpendicular to the center point of the wound, and of high enough resolution to be able to judge wound aspects in detail. The digital photographs of the first 50 patients of the above mentioned clinical trial were selected for the analysis of this study. Besides the bedside evaluation, wounds were also assessed by means of computer-aided image analysis. This assessment, in which the percentage of epithelialization was determined, was performed by three independent observers using the same set of photographs. These observers had not performed the clinical (bedside) evaluation. Fig. 1 shows an overview of the study design.

2.2. Measurements with digital image analysis

Macroscopic quantification of the wounds was achieved using the computer-assisted image analysis software NIS-Elements Ar (Nikon Instruments Europe B.V., Amsterdam, The Netherlands). This semi-automatic software can analyze a digital photograph and measure the number of pixels of the selected area. Independent of each other, the observers first marked the total wound area. The total wound area was the area of the initial burn wound that was transplanted with a SSG. Following this, the observer manually marked the parts of the wound that were not epithelialized or were not covered with a vital SSG, termed open wound area. The marked total and open wound area were calculated and presented by the number of pixels. Wound parameter epithelialization was defined as the percentage of the wound with a vital skin graft and healed graft interstices. Accordingly, necrotic or granulation tissue was interpreted as non-epithelialized. In each

Fig. 1 – Overview of the study design.
wound, the percentage of wound epithelialization was calculated by the following formula:

\[ 1 - \frac{\text{pixels open wound area}}{\text{pixels total wound area}} \times 100\% \]

Fig. 2a–d shows one of the wounds analyzed by means of digital image analysis and Table 1 shows the digital and subjective data of this wound.

2.3 Statistical analysis

Data were analyzed with the statistical program SPSS for Windows 18.0 (SPSS Inc., Chicago, USA). The interobserver reliability of digital image analysis measures the agreement between several observers. Analysis was performed by means of the intraclass correlation. Also the 95% confidence interval was calculated. The two-way-random effect model and the absolute agreement type for a single and average measurement were selected for the calculations of the intraclass correlation coefficient (ICC) [23]. This calculation provides a single measure ICC which is based on a single measurement and an average measure ICC which is based on the average measurements of all observers. A coefficient below 0.4 represents poor agreement, values above 0.75 represent excellent agreement and values between 0.4 and 0.75 stand for fair to good agreement [24]. The standard error of measurement (SE\text{meas}) was used for the calculation of the number of errors between measurements. The coefficient of variation (CV) was calculated using the following formula: 

\[ CV = \frac{SE_{\text{meas}}}{\text{mean}} \times 100 \]

A low CV percentage stands for less variation in error than a high CV. To analyze validity of the subjective epithelialization assessment, this score was compared to the measurements of the digital image analysis, by means of the ICC. The ICC was chosen for this analysis as it reflects both the degree of correspondence and agreement among the two measurement techniques.

3. Results

The first 50 patients of the above mentioned RCT were treated in the Burn Centers of Beverwijk and Rotterdam in the Netherlands and were used for this clinimetrical study. The mean percentage of epithelialization evaluated during a bedside procedure by the clinician was 88.0 ± 13.5% (median 95.0, interquartile range 11.0). The mean percentage of epithelialization measured with digital image analysis by

<table>
<thead>
<tr>
<th>Table 1 – Digital image analysis measurements of a wound by three observers and the subjective clinical assessment.</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient example</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Observer 1</td>
</tr>
<tr>
<td>Observer 2</td>
</tr>
<tr>
<td>Observer 3</td>
</tr>
<tr>
<td>Mean score observers</td>
</tr>
<tr>
<td>Subjective clinical assessment</td>
</tr>
</tbody>
</table>

Data were obtained from the wound shown in Fig. 2.
three observers was 90.0 ± 10.0% (median 92.3, interquartile range 10.4).

3.1. Reliability of digital image analysis

The interobserver reliability of epithelialization measured with digital image analysis was analyzed using the measurements of three observers. The single and average measure ICCs with 95% confidence interval were respectively 0.48 (0.32–0.64) and 0.74 (0.58–0.84), which represents fair to good interobserver reliability. The coefficient of variation was 9.9%, which means 9.9% of the mean (90%) is measuring error.

3.2. Validity of subjective clinical assessment

The percentage of epithelialization assessed during a bedside procedure was compared with the percentage of epithelialization measured with digital image analysis. A good to excellent agreement was found (single measure ICC 0.67 (0.49–0.80), average measure ICC 0.80 (0.66–0.89), 95% confidence interval).

4. Discussion

In evidence-based medicine, valid and reliable tools for the assessment of wound healing parameters are crucial, not only to record the progress of healing, also to compare the effect of applied treatments. The subjective wound assessment is still most frequently used in clinical practice. For this reason, reliability and validity of this assessment should be examined. In clinimetric research, reliability of measurement methods is investigated first, after which validity is tested. Subjective assessment was already shown to be reliable [22]. In this study, we investigated the validity of the subjective assessment of epithelialization. As there is no standard tool to assess epithelialization, we considered assessment with digital image analysis to be the most valid tool. Therefore, we chose to compare the subjective results of epithelialization with digital image analysis in order to test the validity.

An excellent validity, indicated by the high average ICC value, was found for the subjective bedside epithelialization score when compared with the data of the digital image analysis; the two wound evaluation methods were shown to give comparable results. Therefore, we consider the subjective clinical assessment of epithelialization to be a valid tool. In this study design, wounds were evaluated by a variable clinician. The correlation between the two assessments is expected to be higher, if bedside assessment was performed by the same clinician in all cases. The results of this study can be compared with results of several other studies. First of all, a study performed in venous ulcers showed similar results, in their comparison of the subjective scores with the measurements of digital image analysis [25]. However, this system was designed to measure red granulation tissue, and yellow and black necrotic tissue based on a color analysis [25]. In a study of Hauser et al., the subjective evaluation of epithelialization of two observers was correlated with photoplanimetric assessment [17]. The subjective assessment appeared to have a good correlation with the measurements of the photoplanimetry, however statistical analysis was not provided [17].

Finally, visual assessment was compared with computerized planimetry to measure fibrin percentage [26]. Average visual estimations were very similar to the computerized planimetry, therefore bedside evaluation of fibrin percentage was considered to be reliable [26]. Although in our study only the parameter wound epithelialization was investigated, it is plausible that the subjective assessment is also reliable and valid for the evaluation of other wound parameters, such as the percentage of eschar, granulation or necrotic tissue. However, more research is necessary to determine the clinimetric properties of the subjective wound assessment in chronic wounds.

Preceding the correlation of the subjective bedside assessment with the scores obtained by digital image analysis, we tested the reliability of the digital image analysis. Our data show that interobserver ICC values of parameter epithelialization measured by digital image analysis were good, therefore we can safely assume the intraobserver reliability is good as well. Intraobserver reliability is expected to be higher than the interobserver reliability, as there is less bias within one observer [27]. Therefore, in this study only interobserver reliability was tested. In the majority of the reported studies, reliability of other wound parameters and wound types were investigated, however, some studies showed comparable results to ours. In one study, a high agreement was found between observers assessing the percentage of necrosis and granulation tissue using digital image analysis [25]. In addition, Laplau et al. investigated the interobserver reliability of computerized planimetry for measuring fibrin percentage and also found high ICC scores [26].

Fortunately, this study implies that the subjective clinical assessment of epithelialization can be used for clinical purposes, given that assessment with digital image analysis has some shortcomings. Even digital image analysis of epithelialization rate requires some involvement of observers and cannot be entirely automatic; the labeling of the wound aspects still relies on the diagnostic view of the clinician or researcher. Due to the variable aspect of wounds, the system is not capable of distinguishing different wound tissues based on colors totally independently of the observer. Therefore, the observer defines a classification of the wound and determines which parts of the wound are open or non-healed. As it is dependent on the observer’s clinical judgment, the data might show interobserver variability. Nevertheless, digital image analysis has less variability (by using pictures instead of a physical exam which has variable clinical conditions such as different rooms, lighting, and times). This is shown in the standard deviation of the mean percentage of epithelialization assessed with digital image analysis which was lower than the standard deviation of the clinician’s assessment (10.0 and 13.5, respectively). A disadvantage of digital image analysis is that it is time-consuming and therefore, its clinical usefulness in daily practice is limited. In general, both methods have disadvantages, however, we believe the shortcomings of digital image analysis emphasize the importance of investigating the validity of the subjective clinical assessment.

In conclusion, feasible, reliable and valid wound assessment is a must in wound care to evaluate and therefore improve wound treatment. Reliability of digital image analysis
was investigated and shown to be good for the assessment of epithelialization. However, it is relatively time-consuming, and for this reason is less feasible in a clinical setting. After comparison with the data obtained by digital image analysis, subjective clinical assessment was shown to be a valid method to evaluate epithelialization in transplanted wounds. Therefore, we conclude that subjective clinical assessment of epithelialization should be used as the primary measure in clinical trials.

Conflict of interest statement

None.

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