EFFICACY AND TOLERANCE OF CALCIUM ALGINATE VERSUS VASELINE GAUZE DRESSINGS IN THE TREATMENT OF DIABETIC FOOT LESIONS

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SUMMARY - Background: The study aimed at comparing the efficacy and tolerance of an alginate wound dressing with a vaseline gauze dressing in the treatment of diabetic foot lesions.

Methods: This open-label randomized multicenter controlled study was designed to assess the effect of an up to 6-week treatment with either calcium alginate or vaseline gauze dressings. Lesions were either acute or chronic, under cleansing, and with a surface area of 1-50 cm²; osteomyelitis and severe hypovascularization were non-inclusion criteria. Dressings were changed every day then, once granulation had occurred, every 2 to 3 days. Primary outcome was the proportion of patients with granulation tissue over 75% of the wound area and having a 40% decrease in wound surface area; secondary outcomes were pain on dressing changes, the number of dressing changes, and adverse events.

Results: Seventy-seven patients were enrolled. Due to the premature termination of treatment in 13 patients, it was decided to reduce the period of the efficacy analysis to 4 weeks (without revising the criteria of efficacy). The success rate was of 42.8% in the calcium alginate group and of 28.5% in the vaseline gauze group (not significant difference). A subsequent analysis of granulation tissue surfaces covering the wounds at week 4 (all surfaces taken together) showed a superiority of calcium alginate (p = 0.047) and the total number of dressing changes tend to be lower (p = 0.07). Adverse events, which occurred in the calcium alginate group (p = 0.04), were always judged independent of the treatments. Pain on dressing change was lower in the calcium alginate (p = 0.04). A sub-sequence analysis of granulation tissue surfaces covering the wounds at week 4 (all surfaces taken together) showed a superiority of calcium alginate (p = 0.047) and the total number of dressing changes tend to be lower (p = 0.07). Adverse events, which occurred in the calcium alginate group (p = 0.04), were always judged independent of the treatments.

Conclusions: As compared with vaseline gauze, calcium alginate appears to be more appropriate for topical treatment of diabetic foot lesions in terms of both healing and tolerance.

Key-words: diabetes, diabetic complication, diabetic ulcer, wound care, alginate, healing.

RÉSUMÉ - Efficacité et tolérance d’un alginat de calcium pur (Algostéril®) versus un pansement gras (Vaselitulle®) dans le traitement des lésions du pied chez le sujet diabétique.

Contexte : L’objectif de l’étude était de comparer l’efficacité et la tolérance d’un alginat de calcium (Algostéril®) relativement à un pansement gras neutre (Vaselitulle®) dans le traitement des lésions du pied chez le sujet diabétique.

Méthodes : Il s’est agi d’un essai contrôlé, randomisé, et réalisé en ouvert qui projetait d’évaluer jusqu’à 6 semaines les effets des traitements par alginat de calcium ou pansement gras neutre. Une stratification a été réalisée pour séparer les lésions aiguës des lésions chroniques. Toutes ces lésions étaient en voie de détersion et mesuraient de 1 à 50 cm² ; ont été exclues les situations d’ostéite et d’hypovascularisation sévère. Les pansements ont été changés tous les jours initialement, puis tous les 2 à 3 jours à l’apparition d’un tissu de granulation. Le critère principal d’évaluation était la proportion de patients présentant un tissu de granulation couvrant plus de 75 % de la surface de la plaie et une réduction de la surface de la plaie d’au moins 40 % ; les critères secondaires ont été la douleur au retrait du pansement, le nombre total de pansements, et les événements indésirables.

Résultats : Soixante-dix-sept patients ont été inclus. En raison de l’arrêt prématuré du traitement chez 13 d’entre eux, il a été décidé de réduire la période d’analyse à 4 semaines sans réviser pour autant les critères d’évaluation. Le taux de succès a été de 42,8 % dans le groupe alginat et de 28,5 % dans le groupe pansement gras (différence non significative). Une analyse complémentaire de la surface du tissu de granulation couvrant la plaie à la semaine 4 a montré la supériorité de l’alginat de calcium (p = 0.04). Avec l’alginat de calcium, la douleur au changement de pansement s’est avérée moindre (p = 0.047) et le nombre total de pansements était à être moins élevé (p = 0.07). Des événements indésirables sont survenus 4 fois dans le groupe alginat de calcium et 6 fois dans l’autre groupe ; ces événements ont toujours été jugés indépendants des traitements par les investigateurs.

Conclusions : Comparativement au Vaselitulle®, l’Algostéril® semble plus approprié dans le traitement local des lésions de pied dans le diabète, tant pour l’efficacité que pour la tolérance.

Mots-clés : diabète, complications du diabète, ulcère diabétique, soin de plaie, alginat, cicatrisation.
up to 15% of people with diabetes are affected with foot lesions at sometime in their life and such complications can have considerable economic consequences [1-4]. The varying prevalence of these lesions reflects differences not only in demographic and comorbidity risk factors [5] but it is likely that prevalence may also be affected by the wound management strategies employed. Dressings that may be appropriate for foot lesions in the non-diabetic patient may not be suitable for diabetic patients [6]. Indeed, topical antiseptic agents at normal concentrations may interfere with the healing of the diabetic wounds because of their cytotoxic properties [7, 8]. Greasy dressings stick to the wound bed and have been associated with pain during removal as well as healing retardation [7]. Hydrocolloid dressings have been associated with blockade of drainage of exudate, maceration, bacterial overgrowth and exacerbation of any underlying infection [9]. Calcium alginate dressings, derived from seaweed, provide a moistened environment that have been shown to favour the healing process. Indeed, alginate dressings have been successfully used in the treatment of pressure and leg ulcers [10-12]. It has been suggested that the use of alginate dressings may provide an interesting alternative to the commonly employed neutral greasy dressing.

To our knowledge, there have been no reports of well-conducted studies into the particular field of the treatment of diabetic foot lesions with dressings [13-15]. The present randomized controlled trial was conducted in order to compare calcium alginate versus a neutral greasy dressing in terms of both healing efficacy and tolerance. Vaseline gauze was selected as comparator because it is the most frequently used dressing for treating such lesions, at least to our knowledge in France.

METHODS

Before the start of the trial, the protocol was approved by the Ethics Committee of Amiens, France. All patients gave written informed consent.

Study design

The study was an open-label randomized multicenter controlled study designed to assess the effect of on up to 6 weeks treatment with either calcium alginate or vaseline gauze dressings in patients having either acute (less than 2 months) or chronic diabetic foot lesions. Statistics were analyzed independently (Quanta Medical, Rueil Malmaison, France).

Patients

Patients were recruited at 13 centers throughout France (Endocrinology - 8 centers, Rehabilitation - 4 centers, Plastic Surgery - 1 centre). Eligibility criteria were that patients should be aged less than 75 years, suffering from diabetes of either type 1 or 2, and should exhibit a foot lesion in the phase of cleansing which surface area between 1 cm² and 50 cm². Partial cleansing was defined as a granulation tissue surface of less than 50% of the wound area surface. Non-inclusion criteria were: a HbA1c level of more than 10%; presence of clinical infection with redness, swelling, warmth and periwound erythema; osteomyelitis on plain radiography or probing of bone [16]; a tunneled wound; any severe hypovascularization (defined on the basis of transcutaneous pressure of oxygen of less than 30 mm Hg). The number of wound dressings and adverse events were recorded on a weekly basis.

Treatment regimen and follow-up

After confirming the patient’s eligibility, patients were randomly assigned to receive treatment with either calcium alginate (Algosteril, laboratoires Brothier, Nanterre, France) or vaseline gauze (Vaselitulle, Solvay Pharma, Suresnes, France) for up to 6 weeks. Patients were classified according to whether they had acute or chronic lesions. Conservative management was carried out using appropriate pressure-relieving methods. Calcium alginate dressing or vaseline gauze dressing were applied directly to the wound to cover the entire areas. In both treatment groups, nurses were instructed in details by investigators for appropriate dressing design. Dressings should be changed every day initially until thoroughly debridement then every 2 to 3 days, depending of the amount of exudate. No other local treatments were permitted during the study except the use of saline solution, which was unrestricted. Mechanical debridement was authorized as necessary. In both groups, sterile gauze was applied as a secondary dressing. Follow-up visits were scheduled at weeks 1, 2, 4 and 6 to monitor both healing efficacy and safety.

Outcomes

Based on a previous prospective, randomized, controlled trial performed with calcium alginate in the elderly [17], the primary outcome was healing success rate. This was assessed by combining two criteria: the proportion of patients with granulation tissue over 75% of the wound area, and the proportion of patients having a 40% decrease in wound surface area. The secondary outcomes were pain on dressing changes, the cumulative number of dressing changes throughout the study period, and the number of adverse events.
Wound evaluation

At each centre, wound evaluation for all patients was made by the same investigator. The surface area of the selected lesion was measured using the same standardized planimetric method in all centres. This technique involved using a transparent material that was placed over the wound in order to outline the circumference with a dark pen. In patients with plantar neuropathic ulcers, planimetric evaluation was made after debridement of calluses. An independent investigator, blind to the allocated treatment, was assigned to analyse the wound area surfaces. Such analysis was performed two times for each patient and the mean value was retained. In case of difference of 20% or more between two values a third measurement was performed, and the mean of the two closest values was retained. Pain during dressing removal was self-reported using a 10-cm visual analogue scale.

Statistical analysis

The sample size was designed to have 80% power to detect an absolute difference of 25 percent in the success rate between the two groups (45% in the calcium alginate group and 20% in the vaseline gauze group) with a one-sided p value of 0.05. The sample size was thus calculated as being 40 patients per group.

Mean values are given ± SD. Comparisons of general characteristics (Table I) were made using the Cochran-Mantel-Haenzel’s test (CMH test), with classification according to the type of wound (either acute or chronic). For secondary outcomes, comparisons of means were made using ANOVA. All calculations were performed by means of SAS software.

Results

Enrolled patients and follow-up

Seventy-seven patients were enrolled and randomized and 64 completed the trial for the full 6 weeks. Of the 13 patients who did not complete the trial, the reasons for not attending the last study visit (week 6) were 1 consent withdrawal at the first week and 4 adverse events (2 local and 2 general) in the calcium alginate group, 1 ineffective treatment and 1 aggravation at the 4th week, and 6 adverse events (3 local and 3 general) in the vaseline gauze group.

More precisely, local adverse events were: 1 osteitis at week 2 and 1 osteoarthritis at week 4 in the calcium alginate group, 1 wound infection and 1 osteitis at week 2 and 1 wound infection at week 3 in the vaseline gauze group. General adverse events were: 1 cardiac arrhythmia and 1 fatal myocardial infarction in the calcium alginate group, 1 fatal pulmonary embolism at day 1, 1 aggravation of arteriopathy at week 2, and 1 occurrence of renal failure at week 3 in the vaseline gauze group.

Due to the premature cessation of treatment in 13 out of 77 patients and, therefore, the loss of data, it

<table>
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<th>Table I. General characteristics of the study patients.</th>
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<td>Wound surface, cm²</td>
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was decided to shorten the study period of the efficacy analysis to 4 weeks. Importantly, this reduction was not accompanied by a revision of the criterium of efficacy and all patients remained included in the 6-week tolerance analysis study.

Baseline features

Patient characteristics are given in Table I according to treatment group. These characteristics were well balanced across the groups with the exception of the number of peripheral revascularization procedures which was more frequent in the calcium alginate group. However the two treatment groups did not differ in terms of peripheral tissue oxygenation since transcutaneous pressure of oxygen (measured after revascularization) was comparable.

History and etiology of foot lesions are given in Table II according to wound duration, either acute or chronic. Acute lesions affected up to one-third of all patients (27 out of 77), with a mean wound duration of almost one month. More than half of the acute lesions (15 out of 27) occurred postoperatively (surgical excision of necrotic, devitalized, or infected tissue, drainage of abscess, digital, lower- or higher-extremity amputation). Mean duration of chronic lesions was 306 days; half were caused by chronic ulcers. In patients having either acute or chronic lesions, there was no difference in wound duration and wound surface area between the two treatment groups.

Outcomes

Assessment of the primary outcome showed a difference of success rate in favor of calcium alginate (42.8% versus 28.5%), in particular in acute lesions (54.5% versus 23.0%); however differences did not reach the significance level (Figure 1). Pain on dressing change was significantly lower in the calcium alginate group as compared to the vaseline gauze group: respectively 0.3 ± 0.1 and 1.8 ± 0.6 on the 0 to 10 scale (p = 0.047). The total number of dressing changes was also lower in the calcium alginate group: 20 ± 1 versus 23 ± 1, although the difference did not reach the significance level (p = 0.07). There were four adverse events reports in the calcium alginate group, as compared with six in the other. However, all these events were judged as independent of the trial products by the investigators.

Complementary analysis

Because the study period reduction due to premature cessation might have affected the success rate, it was decided to perform a subsequent analysis. At week 4 we re-examined separately the granulation tissue surface covering the wound (i.e. not only those > 75%) and the mean reduction in wound surface area. The distribution of percentages of granulation tissue surfaces appeared significantly different in favor of the calcium alginate group (CMH test: p = 0.04; Figure 2). By contrast, the mean reduction in wound surface area did not differ between the two groups: – 35.7 ± 30.7% in the calcium alginate group versus – 34.9 ± 41.1% in the vaseline gauze group; ANOVA).

<table>
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<th>Table II. History and etiology of lesions.</th>
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<td><strong>Acute lesions</strong></td>
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<td>Wound duration, days</td>
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<td>Wound surface area, cm²</td>
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Etiology (n):
- postsurgery          7  8  3  5
- trauma              2  3  6  3
- iatrogenic          1  0  1  0
- mal perforans       0  0 14 11
- miscellaneous       3  3  2  5
**CONCLUSION**

To our knowledge, this is the first randomized controlled study performed with the objective of assessing the efficacy and the tolerance of topical treatment for diabetic foot lesions. Patients in the two study groups were comparable for each general characteristic with the exception of peripheral revascularization procedures, which were more frequent in the alginate group. This observation was however without clinical impact since transcutaneous oxygen pressure,
that ultimately reflects the vascular status, was almost identical for the two groups.

Because two dressing strategies were compared, the study could evidently not be performed in a double-blind manner. Thus, the non-double blind character may represent a major limitation. However, as already stated, the principal assessment parameter (i.e. planimetric evaluation) was analyzed by an independent observer who was not informed of the treatment allocated. Furthermore, considerable care was taken to avoid the use of unauthorized procedures during the study. Lastly, the characteristics of the study patients were well balanced. For these different reasons, it seems unlikely that the present results are biased.

Due to the significant loss of data between week 4 and week 6, it was decided to shorten the period of observation for the efficacy analysis to 4 weeks. At this time point (week 4), no significant difference appeared in success rate (primary outcome) between the two treatment groups, although the results presented in Figure 1 are suggestive of such a difference. The favorable impression is particularly evident for acute lesions, with a success rate of 54.5% in the alginate group and 23.0% in the other. However the difference did not reach the level of significance and this was probably due to the relatively low number of patients in this subgroup (n = 27). It should not be inferred, nevertheless, that calcium alginate is not superior to the regular gauze. It is important to note that there were two major limitations to demonstrating any superiority for calcium alginate. The first is that although the period of observation was shortened from 6 to 4 weeks, it was impossible to change the primary outcome (granulation tissue over 75% of the wound area, and a 40% decrease in wound surface area). The second reason is that most lesions (two-thirds) were chronic and, therefore, less susceptible than acute lesions to evolve favorably during the rather short follow-up period [18].

Because of these above limitations, additional analysis was performed with separate examination of granulation tissue covering the wound and of the reduction in wound surface area. It appeared that the distribution of granulation tissue surfaces covering the wound was different between the two groups, with more favorable results in the calcium alginate group (p = 0.04).

Regarding secondary outcomes, the low pain rate recorded during dressing changes in both treatment groups was another limitation when trying to discover any differences between the 2 groups. Indeed, due to the long duration of diabetes (mean duration > 15 years) in most patients, it would seem likely that many if not all would have at the very least subclinical neuropathy. Moreover, most patients had chronic lesions, notably neurologic ulcers. Nevertheless the pain rating recorded for the calcium alginate group was lower than that recorded for the other group. The lower number of dressing changes is also in favor of calcium alginate. In the opinion of the investigators, this difference in the number of dressing changes would have probably been even greater. It appeared that nurses did not easily change their habit of making daily dressing changes to these lesions to redressing them less frequently (every 2 to 3 days) once debridement and granulation had taken place, despite investigators’ recommendations. Lastly, no adverse event specifically due to either treatment was reported.

In conclusion, when compared with vaseline gauze, calcium alginate seems more appropriate for topical treatment of diabetic foot lesions in several respects. The study demonstrated better efficacy of calcium alginate in terms of healing, at least with the complementary analysis. The calcium alginate dressing was shown to exhibit better tolerance and required a lower number of dressing changes. This is of importance for cost-benefit ratio because nurse wage and travelling expenses represent the most important cost factor in the topical treatment of diabetic foot lesions [19].

REFERENCES