HOW TO DECREASE THE INCIDENCE OF ESCHAR FORMATION DURING THE USE OF TOPICAL POVIDONE-IODINE OINTMENT IN THE TREATMENT OF BURNS

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SUMMARY. The aim of this study was to prevent eschar formation in thermally injured patients during the use of povidone-iodine ointment by modifying therapeutic protocols depending on normal events in healing process. Sixty thermally injured patients of different age groups, sex, and occupation with different burn sizes were involved in the study, allocated to two groups. Group A was made up of 17 patients treated with topical povidone-iodine ointment in addition to other prescribed drugs according to the burn unit regimen, while group B was comprised of 43 patients treated with topical povidone-iodine ointment for the first four days post-injury followed by topical silver sulphadiazine cream until discharge and with other prescribed drugs according to the burn unit regimen. In both groups the following were studied, using standard methods: oxidative stress parameters; thyroid, liver, and renal function test; microbiology; mortality rate; healing time and economic aspects. It was found that treatment of burn patients with topical povidone-iodine ointment for the first four days post-injury followed by topical silver sulphadiazine cream reduced the incidence of eschar formation from 100% to 2.3%, in addition to maintaining improvement in burn outcome when using povidone-iodine ointment during the full course of treatment. It is concluded that for the modification of treatment protocols in burns designed to obtain normal wound healing and at the same time to avoid the undesirable effects of the treatment given, the use of topical povidone-iodine ointment for the first four days post-injury, followed by topical silver sulphadiazine cream, was a good application. In addition, this study clearly shows the importance of the therapeutic targeting of oxidative stress in burn treatment, especially during the first four days post-injury, a period when blood levels of oxidative stress parameters are at a maximum.

Introduction

The area of research in burn wound management has dramatically increased during the last decades. Rapid burn wound closure and complete healing represent a big challenge for many clinicians because of the close correlation between the burn wound and complications such as multiple organ failure and infection, the commonest causes of burn-related death.[1] Accordingly, in many burn centres great efforts have been made to maintain normal burn wound healing.

The process of wound healing in general represents a dynamic, interactive process involving soluble mediators, blood cells, the extracellular matrix, and parenchymal cells, and has three phases:

1. Inflammatory phase, starting immediately after injury and lasting 1-3 days. The important events in this phase are:
   - vasoconstriction: constricted vessels produce clotting of blood to seal the wound;
   - vasodilatation: more blood and plasma components are brought to the wound site;
   - increased permeability: increased number of white cells travel through the vessel wall to combat foreign bodies;
   - cellular response: white cells ingest bacteria, debris, and dead cells.

The key cells in this phase include monocytes and macrophages.

2. Proliferative phase, starting 3 days after injury. In this phase fibroblasts are key cells playing a main role in granulation, epithelialization, and contracture of the wound.

3. Maturation phase, the last phase. The main event here is remodelling, i.e. strengthening of the scar occurs by the consolidation of collagen fibres, which regain nearly 80% original tissue strength. The key cells in this phase are macrophages and fibroblasts,[2] in addition to which many molecules and other cells and enzymes are also involved in the healing process.

It is important to bear in mind that any disruption occurring during the healing process leads to what is called "abnormal wound healing". Several examples illustrate the multifactorial nature of this condition, such as diabetic ulcers, keloids, and hypertrophic scars.[3]

In our previous work, povidone-iodine ointment (PVP-I) was used topically for burns throughout the course of

treatment in the burn ward, and eschar formation occurred in all thermally injured patients treated according to this regime. This was the only side effect of treatment with topical PVP-I; 10% salicylic acid was successfully used as a keratolytic agent to treat this side effect.

The aim of this study was to decrease the incidence of eschar formation in thermally injured patients by modifying the treatment protocol depending on the mechanisms involved in wound healing, at the same time maintaining improvement in burn outcome.

Patients and method

This study was conducted on 60 patients (28 males and 32 females) of varying age (1.5-70 yr) (31.3 ± 20.6 yr, mean ± SD), with varying burn percentage (10-60%) estimated according to the rule of nines and varying burn degree ranging between first and third. The causes of burn were direct flame (90%) and hot water (10%). The patients were admitted to the burn unit in the Department of Surgery in Baquba General Hospital, Diyala, Iraq, over a period of three months.

The patients were allocated to two groups:

- group A: 17 patients (8 males and 9 females), treated with topical PVP-I in addition to other prescribed drugs and according to our burn unit regime;
- group B: 43 patients (20 males and 23 females), treated with topical PVP-I for the first 4 days post-injury followed by topical silver sulphadiazine cream 1% (SSD) until discharge, plus other prescribed drugs determined by burn unit policy.

In addition, 12 healthy subjects (5 males and 7 females), with the same age range as that of the patients, were selected to serve as control for basic comparison.

In both groups various parameters were measured according to standard methods, including oxidative stress parameters (malondialdhyde [MDA] and glutathione [GSH]), thyroid function test, liver and renal function test, wound swab for microbiological examination, healing time, and costs.

Statistical analysis

1. The results are expressed as mean ± SD.

2. The Student t-test was used to examine the degree of significance, and a p value ≤ 0.05 was considered significant.

Results

The data in *Table I* show that the value of MDA, the product of lipid peroxidation, significantly increased ($p \leq 0.05$) in the serum of burn patients (both groups), compared with the healthy control group. At the same time,

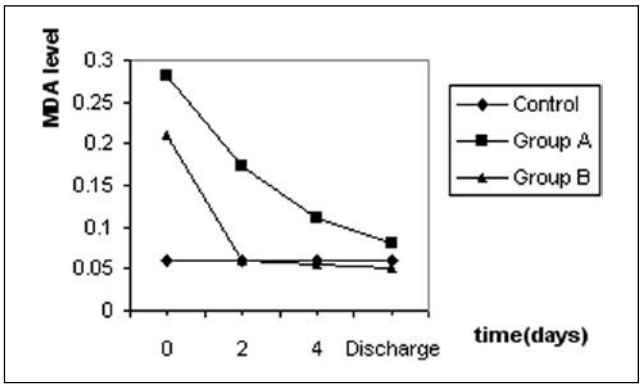

Fig. 1 - Effect of topical treatment in group A and group B on serum level of MDA in burn patients.

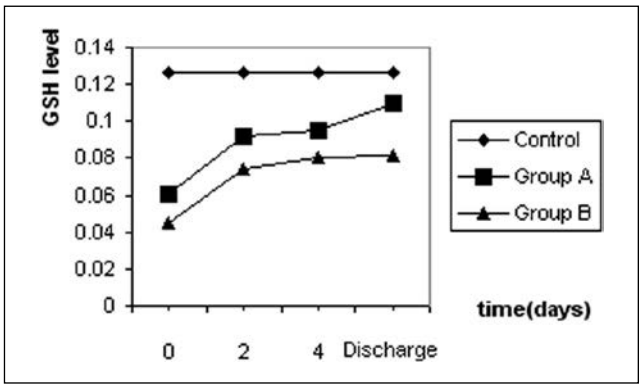

Fig. 2 - Effect of topical treatment in group A and group B on serum level of GSH in burn patients.

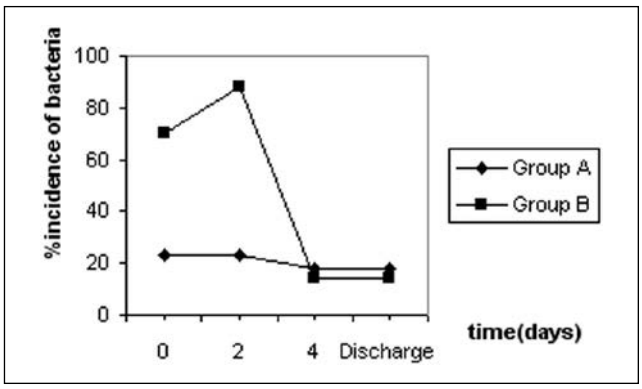

Fig. 3 - Effect of topical treatment in group A and group B on incidence of bacteria isolated from burn patients.

the GSH serum level - the natural antioxidant - significantly decreased ($p \leq 0.05$) in burn patients compared with healthy control.

Treatment with topical PVP-I showed a significant reduction ($p \leq 0.05$) in the MDA level after 2 days (38%) and on discharge day (71%), as well as a significant increase ($p \leq 0.05$) in the GSH level after 2 days (50%) and

Table I - Results of the various treatments

Group	No.	Duration	Plasma MDA µmol/l	Plasma GSH µmol/l	Serum T3 nmol/l	Serum T4 nmol/l	SGPT u/l	SGOT u/l	Serum alk. ph. u/l	Blood urea nmol/l	Serum cr. mmol/l
Control	12	—	0.06 ± 0.02 [a]	0.126 ± 0.018 [a]	1.1 ± 0.2 [a]	8.5 ± 1.7[a]	12.4 ± 1.4[a]	8.6 ± 1.2[a]	61.5 ± 12.4[a]	4.1 ± 0.7[a]	70 ± 15[a]
Group A	17	Zero time	0.281 ± 0.019[b]	0.061 ± 0.011[b]	1.4± 0.2[a]	10.9 ± 2[a]	16.2 ± 2.1[a]	9.3 ± 1.4[a]	50.9 ± 8.5[a]	9.5 ± 1.6[b]	135 ± 29[b]
		2 days	0.174 ± 0.02[c]	0.092 ± 0.02[c]	1.3 ± 0.12[a]	10 ± 1.1[a]	15.5 ± 0.5[a]	10.1 ± 2.1[a]	55.1 ± 7.1[a]	8 ± 1.1[b]	90.5 ± 15[c]
		4 days	0.11 ± 0.03[c]	0.095 ± 0.01[c]	1.35 ± 0.2[a]	9.9 ± 1.7[a]	15.1 ± 1.3[a]	12.2 ± 3.3[a]	52.5 ± 8.5[a]	7.2 ± 1.6[c]	81.1 ± 17.6[c]
		Discharge day	0.08 ± 0.01[d]	0.11 ± 0.03[d]	1.2 ± 0.4[a]	9.7 ± 1.9[a]	14.1 ± 1.9[a]	10.9 ± 2.2[a]	49.1 ± 5.6[a]	5.1 ± 2.3[d]	72.5 ± 12.8[d]
Group B	43	Zero time	0.21 ± 0.01[b]	0.045 ± 0.01[b]	1.33 ± 0.2[a]	10.5 ± 1	10.3 ± 1.5[a]	8.8 ± 1.6[a]	67.5 ± 9[a]	6.1 ± 1.5[a]	78.1 ± 12[a]
		2 days	0.06 ± 0.02[c]	0.074 ± 0.02[c]	1.4 ± 0.22[a]	9.7 ± 1.2[a]	14.1 ± 2.5[a]	10 ± 1.2[a]	65.5 ± 9.1[a]	5.8 ± 1.1[a]	80.2 ± 11.2[a]
		4 days	0.055 ± 0.01[c]	0.08 ± 0.01[c]	1.5 ± 0.3[a]	10.9 ± 2.2[a]	12.5 ± 1.1[a]	9.5 ± 1.6[a]	62.4 ± 8.4[a]	4.9 ± 2.1[a]	75.6 ± 7.8[a]
		Discharge day	0.05 ± 0.01[c]	0.082 ± 0.02[c]	1.2 ± 0.25[a]	10.5 ± 2.1[a]	10.1 ± 1.7[a]	9.6 ± 1.7[a]	56,6 ± 7.7[a]	4.6 ± 1.5[a]	76.4 ± 8[a]

Group A: burn patients treated with topical povidone-iodine ointment in addition to other prescribed drugs.
Group B: burn patients treated with topical povidone-iodine ointment for the first 4 days post-injury followed by topical silver sulphadiazine cream in addition to other prescribed drugs.
Results represent mean ± standard deviation.
Results with non-identical superscripts were considered significantly different ($p < 0.05$).
Zero time represents time of resuscitation.

on discharge day (80%), compared with pre-treatment values (*Figs. 1, 2*).

Treatment with PVP-I for the first 4 days post-injury followed by topical SSD until discharge (group B) significantly reduced ($p \leq 0.05$) the MDA serum level after 2 days by 71% compared with pre-treatment values; also, the GSH serum level increased significantly ($p \leq 0.05$) after 2 days by 64% compared with pre-treatment values (*Figs. 1, 2*).

Table I also shows that treatment with topical PVP-I throughout the course of treatment course and treatment with topical PVP-I for the first 4 days post-injury, followed by topical SSD, had no significant effect on serum levels of thyroid hormones T_3 and T_4 or liver enzyme activities compared with control and pre-treatment values. In contrast, blood urea and serum creatinine were significantly elevated ($p \leq 0.05$) in group A at zero time compared with control, and decreased significantly ($p \leq 0.05$) after 2 and 4 days, returning to normal levels at discharge day, compared with pre-treatment. In group B there were no significant changes in the renal function tests.

Table II shows the incidence of the invading bacteria isolated from the burn patients. The percentage of positive swabs decreased from 23.5% to 17.6% in group A, while in group B the percentage increased from 70% at zero time to 88% after 2 days and then decreased to 14% after 4 days and at discharge day (*Fig. 3*).

Table III shows that there was no significant change between the treated groups regarding mortality rate, healing time, and costs.

Table II - Effects of treatment of group A and group B on the incidence of invading micro-organisms isolated from burn patients

Group	No.	Duration	Number of negative swabs	Number of positive swabs
Group A	17	Zero time	13 (76.5%)	4 (23.5%)
		2 days	13 (76.5%)	4 (23.5%)
		4 days	14 (82.4%)	3 (17.6%)
		Discharge day	14 (82.4%)	3 (17.6%)
Group B	43	Zero time	13 (30%)	30 (70%)
		2 days	5 (12%)	38 (88%)
		4 days	37 (86%)	6 (14%)
		Discharge day	37 (86%)	6 (14%)

The most important result obtained in this study was the reduction in the incidence of eschar formation: the percentage of eschar incidence dropped from 100% in group A to 2.3% in group B, which is a very beneficial and wonderful result.

Discussion

During cutaneous thermal injury, several factors contribute to further tissue damage, among which oxygen free radicals are important.[4] The relationship between the amount of products of oxidative metabolism and natural

Table III - Effects of treatment of group A and group B on healing time, incidence of eschar formation, mortality, and cost in burn patients

Group	Number of patients	Healing time (days)	Incidence of eschar formation	Mortality rate	Cost (Iraqi dinars)
Group A	17	8.8 ± 3.6[a]	17 (100%)	1 (5.88%)[a]	62,000 ± 7800[a]
Group B	43	9.2 ± 1.6[a]	1 (2.3%)	3 (6.97%)[a]	55000 ± 6500[a]

Group A: burn patients treated with topical povidone-iodine ointment in addition to other prescribed drugs.
Group B: burn patients treated with topical povidone-iodine ointment for the first 4 days post-injury followed by topical silver sulphadiazine cream in addition to other prescribed drugs.
Results represent percentage of total or mean ± standard deviation.
Results with non-identical superscripts were considered significantly different ($p < 0.05$).
Zero time represents time of resuscitation.

scavengers of free radicals determines the outcome of local and distant tissue damage and further organ failure in burn injury.[5]

In normal body conditions there exists a balance between free radicals and the natural scavengers of the body, while in a traumatic state the balance is lost and reactive oxygen metabolites are greater in number.[6] An increased generation of oxygen free radicals in the extracellular space is seen in inflammatory states, in which the relatively low concentrations of enzymatic and non-enzymatic antioxidants increase the susceptibility of extracellular components to oxygen radical injury.[7] The level of these free radicals in the plasma of patients with thermal skin injury increases in the first few hours post-burn, reaching peak level on day 3 post-burn,[8,9] i.e. during the inflammatory phase of wound healing.[3] At this stage the therapeutic application of antioxidants becomes essential.[10]

Table I shows that the treatment of thermally injured patients with topical PVP-I caused a significant reduction ($p \leq 0.05$) in plasma levels of MDA after 2 days and at discharge day, as well as a significant increase in plasma levels of GSH after 2 days and at discharge day, compared with pre-treatment values.

On the other hand, treatment with topical PVP-I for the first 4 days post-injury, followed by topical SSD, significantly reduced ($p \leq 0.05$) MDA levels after 2 days, which remained around this level until discharge day (*Fig. 1*); also, GSH levels increased significantly ($p \leq 0.05$) after 2 days, compared with pre-treatment values (*Fig. 2*). These data strongly indicate the antioxidant effect of topical PVP-I in burns treatment, the result we obtained in our previous work.[11] The mechanism by which PVP-I exerts its antioxidant effect appears to be due to its iodine content.[12] It has been hypothesized that there is a general antioxidant action of iodide together with peroxidases in all living organisms with iodine-concentrating cells, from primitive algae to recent vertebrates,[13,14] i.e. iodine leads to an increase of peroxidase-activity and therefore to an increased total antioxidant status.

Figs. 1 and *2* show that there was a non-significant reduction in MDA levels during use of SSD and a non-significant elevation of GSH levels; these results are consistent with those obtained by Nagane et al.,[15] who found that the rate of decrease in serum lipid peroxidation product levels was faster during honey therapy than with that observed with SSD treatment. The mechanism of SSD involved in this reduction of MDA levels of elevation in GSH level, even at non-significant level, when compared with pre-treatment levels, is still unknown and requires further investigation.

The results presented in *Table I* clearly show that treatment of burns with topical PVP-I had no effect on thyroid function represented by serum T_3 and T_4, a finding consistent with that obtained by Balogh et al.[16] Regarding liver enzymes, *Table I* shows no significant changes in their activity in both the groups treated compared with control, indicating that these regimes had no effect on the liver function test.[17] Regarding blood urea and serum creatinine levels, which were measured as a renal function test, *Table I* shows a significant increase in these measurements at the time of admission in group A, followed by a gradual reduction until return to normal levels, a change that did not occur in group B.[18] These data clearly indicate the thyroid, liver, and renal safety of treatment with topical PVP-I or SSD in burn patients.

Table II shows that the incidence of wound infection in burns was 23.5% in group A and 70% in group B, at zero time. After 2 days this percentage either remained constant, as in group A, or increased, as in group B (*Table II* and *Fig. 3*). On day 4 this percentage fell to 3% in group A and 6% in group B, remaining constant until discharge day. Treatment with topical PVP-I thus effectively controlled the incidence of infection in group A, while in group B treatment of burns with topical PVP-I for the first 3 days caused a sharp reduction in the infection incidence to a level that was maintained by using topical SSD after the first 4 days until discharge day.

Infection is one of the most frequent complications of the wound healing process, and infection control is therefore very important not only in preventing secondary infection but also in maintaining a correct wound healing process.[19] The use of topical antimicrobial agents is thus very important and rational, especially in the treatment of burns. PVP-I, which is iodine complexed with polyvinyl pyrrolidone, is a widely used and highly potent antiseptic that eradicates all classes of pathogens responsible for noso-

comial infections, including Gram-positive and Gram-negative bacteria, as well as antibiotic-resistant strains and spores (bacterial and fungal), viruses, mycobacteria, and protozoa.[20] As iodine liberated from the PVP molecule, it exerts its antimicrobial effect in less than a minute, with most organisms being destroyed in 15 to 30 seconds or less;[21] the mechanisms involved in these effects include an irreversible combination of iodine with tyrosine residues of proteins, interference with the formation of hydrogen bonding by some amino acids and nucleic acids, oxidization of sulphydryl groups, and reaction with sites of unsaturation in lipids.[22] All these advantages make PVP-I a good candidate for the topical treatment of burns.

One per cent SSD has been commonly used as a topical agent after burn injury:[23] it has a broad antimicrobial activity against Gram-positive and Gram-negative bacteria as well as against yeast.[24] Sufficient data have been reported demonstrating the mechanism of action of SSD on bacteria, where it acts only on the cell membrane and cell wall to produce its bactericidal effect.[25-27] Therefore, from the microbiological point of view, SSD appears to be a good alternative to use following PVP-I, which is employed in the first 4 days post-injury.

Table III shows that there was no significant change in healing time between group A and group B (by healing time we mean the time required for complete healing of the burn wound without any sign of infection).[28] Conversely, when healing is discussed as a process and event, the situation was completely different. As shown in *Table III*, the incidence of eschar formation was 100% in group A, in which PVP-I ointment was used topically during the full course of treatment; this percentage fell to 2.3% in group B, in which PVP-I was used for the first 4 days, followed by topical SSD cream, with eschar formation occurring in only one patient. The formation of eschars after use of PVP-I in burn patients can be easily treated with the application of 10% salicylic acid without any complications and avoiding surgical escharotomy. In an attempt to prevent eschar formation, PVP-I was used for the first 4 days post-injury followed by SSD, as in group B, with excellent results (*Table III*).

There is considerable controversy concerning the effect of PVP-I on wound healing with regard to both *in vitro* and *in vivo* studies. While Kietzman[29] and Vogt et al.[30] reported an improvement in the healing process when using PVP-I, Niedner[31] found that PVP-I did not prolong the total wound healing time. In contrast, Kramer[32] reported in his review that in most instances PVP-I did not effectively promote good wound healing and that most studies showed impaired wound healing. It has been found that low concentrations of PVP-I are toxic to keratinocytes,[33] fibroblasts,[34] and collagenolytic enzymes:[35] these cells and enzymes are most prevalent in the proliferative and maturation phases of wound healing.[3]

Thus, according to these trials, PVP-I disturbs the delicate balance existing in the wound healing process during the middle to late stage of healing, leading to abnormal wound healing. Also, wounds are generally more susceptible to infection in the inflammatory phase of healing.[2] All these considerations mean that PVP-I is best used in the first 4 days post-injury followed by other topical antimicrobial agents such as SSD, which has no such effect.

Furthermore, during the inflammatory phase, reactive oxygen species reach peak level, and this is the time to use a topical antioxidant like PVP-I to improve burn outcome.[36,37]

On the other hand, SSD has been shown to be absorbed significantly from large burn wounds when used topically, increasing the probability of silver toxicity, especially during the inflammatory phase when blood vessels dilate and permeability increases.[38] Dogra[39] showed that treatment with SSD can cause leucopenia during the first week after burn injury owing to its effect on bone marrow toxicity, while Nicholas et al.[40] reported that silver accumulation in the liver leads to inhibition of glutathione peroxidase. The use of antioxidants in the inflammatory phase therefore plays an important role in decreasing microvascular permeability, where free radicals also have a large role to play,[36] resulting in reduced absorption of silver and preventing silver accumulation and toxicity. All this information, when integrated, will support our protocol for the treatment of burn patients, i.e. topical use of PVP-I for the first 4 days post-injury, followed by topical SSD cream until discharge.

Reduction in the mortality rate remains the main goal of many clinicians during the treatment of burns, and numerous therapeutic approaches and considerable effort have been devoted worldwide to the achievement of this goal. Oxidative stress has been reported recently as an important modifier of the mortality rate of burn patients:[41] since reactive oxygen species play an important role in the genesis and development of post-burn multiple organ failure - the primary cause of death in burns[42] - interference with these free radicals is of great value in the improvement of the burn patient mortality rate, which requires the use of antioxidants, especially during the first 4 days, the period when the blood levels of oxidative parameters are at their maximum.[8] This may explain the results reported in *Table III*, where topical PVP-I was used for 4 days post-injury, compared with 87.5% - the mortality rate in burn patients treated without antioxidants, as reported in our previous work.[11]

Table III also shows that the cost of treatment of burn patients in group B was non-significantly reduced compared with the cost of treatment in group A. This reduction may have been due to the modification in topical treatment: in group B the incidence of eschar formation fell to 2.3%, compared with group A, where it was 100%. On

the other hand, microvascular permeability, and consequently fluid leakage and loss, increased as a result of the reactive oxygen species generated by thermal injury, as shown by Youn et al.[43] The use of PVP-I as an antioxidant, in addition to its broad-spectrum antimicrobial effect, interferes with the reactive oxygen species, decreasing microvascular permeability and fluid loss and leading to a significant reduction in costs, as previously found,[11] compared with groups of patient whose treatment did not include antioxidants. Moreover, this decreased fluid requirements from 4 ml x weight (kg) x percentage burn to 2 ml x weight (kg) x percentage burn. Costs fell significantly.

Another important point is that when microvascular permeability was reduced, this led to decreased oozing, which reduced the frequency of bedclothes changing from once daily to every other day or more (drying effect); this effectively reduced costs calculated on a per course basis.

Conclusion

The treatment of burn patients with topical antioxidants such as PVP-I for the first 3 days post-injury, followed by topical SSD cream, reduced the incidence of eschar formation from 100% to 2.3%, a result achieved by modification of our treatment protocol without affecting other actions of PVP-I when used during the whole course (including antioxidant effect; thyroid, liver, and renal safety; incidence of infection; mortality rate; healing time and costs) compared with another group in which PVP-I was used for the first 4 days, followed by topical SSD cream.

This modification was designed in order to obtain normal wound healing and at the same time to eliminate the undesirable effects of PVP-I and SSD when used at unsuitable times during burn wound healing.

This study also demonstrated the rational use of antioxidants and the importance of the therapeutic targeting of oxidative stress in the treatment of burns.

RÉSUMÉ. Les Auteurs de cette étude se sont proposés de prévenir la formation des escarres dans les patients traités avec l'emploi de l'onguent de povidone-iodine, modifiant les protocoles thérapeutiques selon les événements normaux du procès de la guérison. Soixante patients atteints de lésions thermiques de divers âge, sexe et occupation qui présentaient des brûlures de diverse extension ont été inclus dans l'étude, divisés en deux groupes. Le groupe A était composé de 17 patients traités avec l'onguent de povidone-iodine topique en plus des autres médicaments prescrits par le régime de l'unité des brûlures, tandis que le groupe B comprenait 43 patients traités avec l'onguent de povidone-iodine topique pendant les quatre premiers jours après la lésion, suivi par la crème topique de sulfadiazine argentique jusqu'à la sortie de l'hôpital, et avec les autres médicaments prescrits selon le régime de l'unité des brûlures. Dans tous les deux groupes les Auteurs ont étudié les aspects suivants, utilisant les méthodes normales: les paramètres du stress oxidatif; le test de la fonction thyroïdienne, hépatique et rénale; la microbiologie; le taux de mortalité; le temps de la guérison et les facteurs économiques. Ils ont trouvé que le traitement des patients brûlés avec l'onguent de povidone-iodine topique pendant les quatre premiers jours après la lésion, suivi par la crème topique de sulfadiazine argentique, réduisait l'incidence de la formation des escarres de 100% à 2,3% et maintenait l'amélioration des résultats finals quand ils utilisaient l'onguent de povidone-iodine pendant le cours entier du traitement. Ils concluent que pour la modification des protocoles de traitement des brûlures désignés pour obtenir une guérison normale des lésions et en même temps pour éviter les effets indésirables du traitement pratiqué, l'emploi de l'onguent de povidone-iodine topique pendant les quatre premiers jours après la lésion, suivi par la crème topique de sulfadiazine argentique, était une bonne application. Cette étude démontre clairement en outre l'importance de cibler pour raisons thérapeutiques le stress oxidatif dans le traitement des brûlures, particulièrement pendant les premiers jours après la lésion, c'est-à-dire un période quand les niveaux hématiques des paramètres du stress oxidatif sont au maximum.

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