CLINICAL EVALUATION OF SUTILAINS (TRAVASE) IN THE ENZYMATIC DEBRIDEMENT OF BURN ESCHAR

by

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University of British Columbia 1968

A Thesis Submitted in Partial Fulfillment of
the Requirements for the Degree of
Master of Science

in the Department of
SURGERY

We accept this thesis as conforming to the
required standard

The University of British Columbia
September 1975

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ABSTRACT

The early enzymatic debridement of burn eschar and subsequent skin grafting can greatly reduce patient morbidity, mortality, and also decrease total hospitalization. Since the 1940's, a succession of enzymes from various sources have been carefully evaluated and reviewed both in vitro and in vivo, and been rejected because of inadequate effect or excessive complications. Bacillus subtilis protease, the most recent agent to be developed, has been extensively studied in vitro and recently been released for clinical use in the United States and Canada. To date, in vitro investigation has established it as an effective proteolytic agent, and early in vivo investigation results, primarily under the auspices of the developing laboratory (Flint), are remarkable for their lack of complications and effectiveness of debridement. Preliminary use of this agent at the Vancouver General Hospital Burn Unit indicated a higher complication rate than those previously reported. The purpose of the study was then to clinically evaluate the debridement of burn eschar by Travase and to evaluate the complications encountered.

Travase therapy was begun on selected cases as soon as possible after initial resuscitation and stabilization of the burn patient had been completed. Areas selected were less than 15% Body Surface Area (BSA) and generally of functional importance such as the hand. The Travase was applied three times daily in ointment form over the eschar and covered with moist saline mesh dressings as recommended by the manufacturer. In selected control cases, areas of clinical mirror image burns or adjacent burns of similar depth, were treated identically

except for the application of the enzyme. Photographic records were maintained of the progression of debridement and the Travase was continued until debridement was complete, judged ineffective, or complications necessitated discontinuance of therapy. A total of 25 cases were evaluated, 5 of which had areas of similar burn treated identically, except for the use of Travase, serving as areas of comparison.

Adequate debridement judged as completion of debridement within two weeks of initiation of therapy occurred in 65% of overall cases. Treatment begun within 48 hours of burn injury debrided faster clinically than older, more leathery eschar.

The incidence of complications and discontinuation noted was higher than previous studies, namely 28% of 25 cases were discontinued, and all but 3 cases of 25 had some complication. Pain on application was more common than previously reported and a major source of patient dissatisfaction. Concurrent burn wound sepsis with Travase application occurred in 25% of cases, but may be controlled in some cases by concurrent use of a topical antimicrobial, although this was not controlled.

Overall, clinical results were judged satisfactory in limited clinical situations, specifically, small local areas of full thickness burn in otherwise healthy patients, or functional areas such as the hand in larger, otherwise stable burns. The results of this study reveal the need for caution in clinical use of Travase not sufficiently emphasized in the previous literature and emphasize its adjunctive role to conservative management.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CLINICAL EVALUATION OF SUTILAINS (TRAVASE) IN THE ENZYMATIC DEBRIDEMENT OF BURN ESCHAR

INTRODUCTION

The ultimate aim of all burn therapy is a rapid, safe removal of burn eschar followed by early skin grafting and a return to full function.[1] Early removal of all devitalized tissues and early skin grafting greatly reduce hospital stay and morbidity of patients with small to moderate sized third degree burns. The early debridement of large third degree burns has been undertaken by some surgeons in an attempt to decrease the severity of septic complications so often encountered in these patients, with varying degrees of success until recently. New enthusiasm for staged eschar excision with scalpel, dermatome blade, electrocautery, and laser beam[2,3] has also stimulated new evaluations of the enzymatic debridement of burn wounds.

The clinical interest in topical enzyme therapy for burns appears to wax and wane, as with most agents in medicine, in direct relationship to its effectiveness and its complications. Various enzyme preparations have been the subject of much research investigation and have been used as a clinical tool in a myriad of disease processes since the late 1940's. Early investigators set forth certain criteria for an ideal wound debridement agent listed as follows. The enzyme:

1) should be capable of rapid lysis of fibrin, denatured collagen, elastin, and exudate as these are the primary tissue protein components in the burn eschar.
2) should be inactive in contact with viable tissue.
3) should be non toxic and non irritating to the wound.

4) should be easily prepared, stable, and readily applicable to most lesions.

REVIEW OF LITERATURE

Many agents were developed that fulfilled the above criteria with varying degrees of success. In 1950 Tillett[4] and co-workers reported the use of streptococcal enzymes as a debriding agent. Connell, et al.[5,6,7] have repeatedly advocated enzymatic debridement of burn wounds with streptococcal enzymes, a plant proteinase ficin (Debricin) and other less defined fungal or bacterial proteases. Altemeier, Humel and MacMillan[8,9] have, since 1951, performed a series of in vivo and in vitro experiments on several clostridial enzymes including clostridium histolyticum and pertussins as well as enzymes of E. coli, pseudomonas aeruginosa, B. proteus and a mixture of enzymes from the papaya fruit. Burke and Golden,[10] in 1958, used a papain enzyme in combination with urea and chlorophyll. However, over the years, careful follow-up and review have proved all to be highly over-rated as to effect, or fraught with side effects.[9,11]

In the early 1960's a new broad spectrum proteinase was derived by the filtration of Bacillus subtilis ferment toxins and subsequently named "Sutilains." The sterilized preparation is homogenized into a hydrophobic ointment base, in a standard concentration. It functions at a pH range 5.0 to 6.8 optimum, is easy to apply in ointment form, and can be stored for 18 months at 2 degrees - 10 degrees centigrade.[16] Prytz, et al.,[13] using debrided burn wound eschar in a dilute enzyme solution measured quantitative loss over 24 hours by weight of the eschar and qualitative loss by tyrosine and hydroxyproline measurement of the

supernatant. They found a 38% digestion of eschar in 24 hours with some further increase up to 120 hours. The enzyme favored complete digestion to amino acids although incomplete digestion of burn eschar was also seen. Similar work with normal split skin grafts revealed a loosening of the epidermal layer morphologically and an amount of tyrosine formed 1/7 of that formed from eschar, indicating some activity on viable tissue. Using similar techniques, Silverstein, et al.[17] compared Sutilains to several other proteolytic agents: papain, chrymopapain, trypsin and chymotrypsin, and found it to be the most effective against eschar proteins but relatively less effective than collagenase against intact collagen.

Toxicologic animal trials performed by Flint Laboratories[10] found dermal irritation consisting of edema and erythema after 21 days of continued use. Systemic and local anaphylaxis were negligible. Immunologically Travase was inactive on skin application and no teratogenecity was found.

Initial clinical investigation,[12] primarily under the auspices of the developing laboratory (Flint), evaluated the use of the enzyme in four categories of surface wounds--necrotic wounds, decubitus ulcers, peripheral vascular ulcers, and burns. Garrett[12] studied 420 such cases including 101 acute burns with a range of effective debridement from 71-99%. Effective debridement was defined as significant lysis of necrotic elements in 5 to 7 days; but little patient data, method of evaluation or control was provided. Connell[13] found similar good results with 93% of 72 acute burns satisfactorily debrided, but cases were not individualized as to type of lesion and the burns were not documented as to size. Pennisi, Capozzi and Friedman,[14] in a recent paper, stated that results were dramatic--85% of

68 patients effectively debrided and that Travase was locally and systemically safe. However, they did not document the size of the burns treated. It would appear that some of the patients did have sepsis, but they were unable to relate this to Travase. Other side effects reported by these papers have been minimal, consisting of slight transient burning pain, parasthesias, occasional mild dermatitis, and minor bleeding. Garrett, in 420 patients evaluated, had a discontinuance rate of only 1.6%. However, since the initiation of this project, Altemeier,[9] in evaluating 11 patients, has retrospectively associated Travase and early post burn bacteremia and septicemia in 64%. Krizek[15] has also suggested that the Travase may be conducive to burn wound sepsis.

PURPOSE OF THE STUDY

Our preliminary results also suggested a considerably higher complication rate than those previously reported. Our intention was:

1) to clinically evaluate the debridement of burn eschar by Travase,
2) to evaluate the complications encountered.

MATERIALS AND METHOD

Of 54 burns admitted to the burn ward at the Vancouver General Hospital over an eight month period, 25 were selected for Travase use. Included in these 25 cases were 5 cases in which a clinical control was possible. Three patients had clinical mirror image burns and Travase was used on one limb while a control saline dressing was used on a clinically identical burn on the other. An additional 2 patients had individual clinically homogeneous areas of full thickness burn divided in two, and

Travase applied on one half of the area under the same saline dressing. Control areas treated with saline were not included in the final results.

Travase therapy was begun, in the majority of cases within 7 days post burn, after the initial fluid resuscitation and stabilization of the patient had been completed. Onset of therapy ranged from 24 hours post burn to 27 days post burn. Attempts were made to start the therapy as soon as possible and 25% of the cases were started within 48 hours of burn. Ages ranged from 16 to 71 years (Table I). The majority of the burns were of flame origin, either from house or clothing fire, or propane explosion. Three electrical and 2 hot metal burns were included (Table II). The areas treated totalled 33 in 25 patients.

An area of clinical full thickness burn was selected measuring less than 15% of body surface area (BSA), as recommended by the experience of others.[5,12,13,14] The Travase was applied every 8 hours under saline compresses of fine mesh burn gauze, moistened hourly. Photographic records were maintained of the progression of debridement. The patients were tubbed daily in a Hubbard tank at which time any loose debris was mechanically removed. Certain detergents, antiseptics or compounds containing specific metallic ions such as Betadine or hexachlorophene were avoided as they have been reported as inhibiting the enzymatic action of Travase.

Sites treated were primarily areas of functional importance, the dorsum of the hand and forearm being the most common (Table III). Total areas burned ranged from 6-65% BSA.

The Travase was maintained until debridement was complete if the patient remained stable, usually 3-14 days. The remainder of the burn was

treated by exposure or the application of topical Garamycin as the situation dictated. Development of a clinical septic state or obvious purulent drainage under the occlusive dressings necessitated discontinuance of the Travase or alteration with similar Garamycin dressings. Severe pain, uncontrolled with Talwin analgesia or severe bleeding in the area of Travase application also necessitated discontinuance of therapy.

All patients were grafted as soon as possible after completion of debridement, but this did not necessarily coincide with cessation of Travase therapy.

TABLE I

PATIENT DATA

Number of Patients: 25

Sex: 23 Male 2 Female

Age:	0-10	11-20	21-30	31-40	41-50	>50
	0	3	7	9	0	6

TABLE II

BURN DATA

Type Burn	
Electrical	3
Flame	20
Metal	2
Total	25
B.S.A. Burn	
$<10\%$	2
11-30%	14
31-50%	5
$>50\%$	4
Total Burns	25

TABLE III

TREATMENT AREA DATA

Area Treated	
0- 5%	24
6-10%	7
11-15%	2
Total	33
Site Treated	
Dorsum hand and arm	22
Axilla	2
Chest/Abdomen	2
Lower Extremity - Joint	2
- Flat Surface	5
Total	33

RESULTS

Clinical Trial

The overall rate of completion of debridement regardless of the time post burn that treatment was begun is listed in Table IV. Adequate debridement within two weeks of initiation of therapy occurred in 21 of 33 areas treated or 65%. Ten of these 21 cases were ready for grafting within one week of beginning Travase therapy. Overall, 7 cases were discontinued for a variety of reasons listed below, and in 5 cases therapy was inadequate or assessment not possible.

Of those areas in which therapy was begun within one week of burning (22/33), 30% were ready for grafting within a further week and 13 of 22 were ready for grafting within two weeks of the burn. All seven discontinued cases were within this group. Those cases started after a week post burn required a longer time from initiation of therapy to time of grafting (Table V). Cases begun within 48 hours numbered only 8, but clinically debrided faster and as suggested by the table, were ready for grafting at an earlier date.

Control Cases

Control cases were selected for comparable mirror image or adjacent area burns. Five cases were selected over a 6 month period, 4 started on Travase within 48 hours of burning and 1 four days post burn. Three hand or arm burns were used as mirror image controls: adjacent full thickness electrical burn on a buttock and a burn of forearm and arm were areas treated under a common dressing.

Two cases as examples are listed below with sequential photographs.

TABLE IV

RATE OF DEBRIDEMENT - OVERALL

Complete one week	10
Complete one to two weeks	11
Incomplete or inadequate	5
Discontinued	7
Total Areas	33

TABLE V

DEBRIDEMENT COMPLETION

Time from burn to initiation of Travase

<48 hours	8
2- 7 days	14
8-14 days	11
>15 days	0

Time from initiation of Travase to suitable for grafting

	Discontinued	0-7 d.	8-14 d.	15-21 d.	Unable to assess or inadequate	Totals
<48 hours	3	3	1		1	8
2- 7 days	4	4	5		1	14
8-14 days		3	5		3	11
Totals						33

Case 1 represented a good initial result, but a burn wound infection developed while on Travase therapy. Case 2 showed good initial debridement but was incomplete at time of operative debridement due to the extension of burn into muscle layers.

Case 1 - 16 year old boy with full thickness electrical burn, total 3% BSA over right buttock and thigh. Travase was begun 2 days post burn (Figure 1) and continued 12 days prior to excision of Travase area (Figures 2, 3, 4).

Case 2 - 58 year old alcoholic with hot metal fourth degree burns to both arms. Travase was begun 2 days after burn to right arm while left arm of similar depth was compressed with saline alone (Figures 5, 6). Incomplete results excised 7 days after beginning Travase (Figures 7, 8, 9).

Complications

Local burning pain of a minor to moderate nature not present under saline dressings alone, controlled by analgesic, was noted in 12 of 25 cases and in a further 3 cases resulted in discontinuance of therapy (Table VI). Iced saline compresses were used in an attempt to alleviate pain with little demonstrable result. Bleeding while under saline compress spontaneously occurred in 3 cases and was of a severe nature in 1, but all were easily controlled with pressure. Bleeding of this nature was not seen clinically, except with the Travase treatment. Development of a septic state while on Travase diagnosed by the presence of a spiking temperature, confusion, tachycardia and increased wound drainage under the Travase dressings occurred in 8 of 25, or 35%. In 3 of these 8 cases, the sepsis was controlled by alternate Garamycin dressings, but because of the clinical status was discontinued in 5. Only 3 patients had no complaint or objective complication.

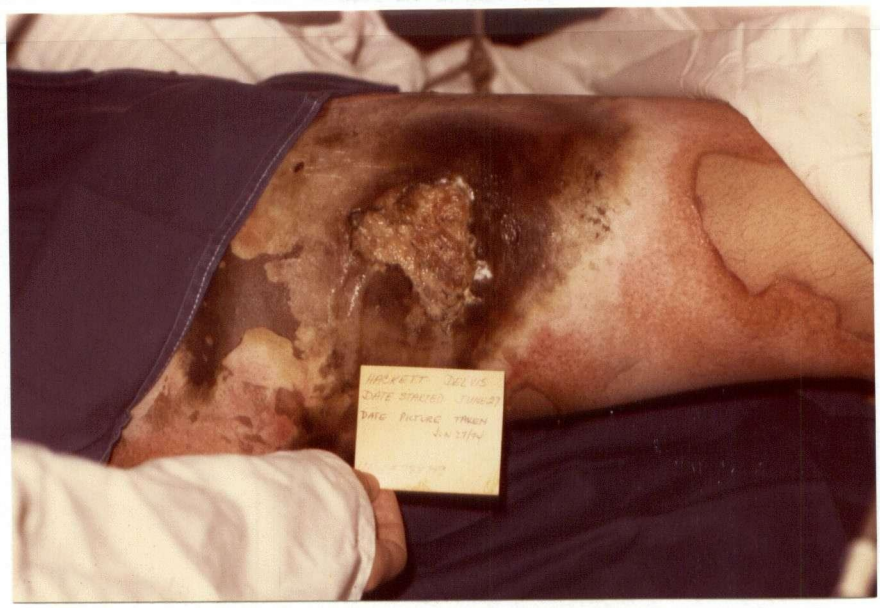

Figure 1

16 year old boy with 3% BSA electrical burn right thigh. 2 days post burn prior to initiation Travase treatment.

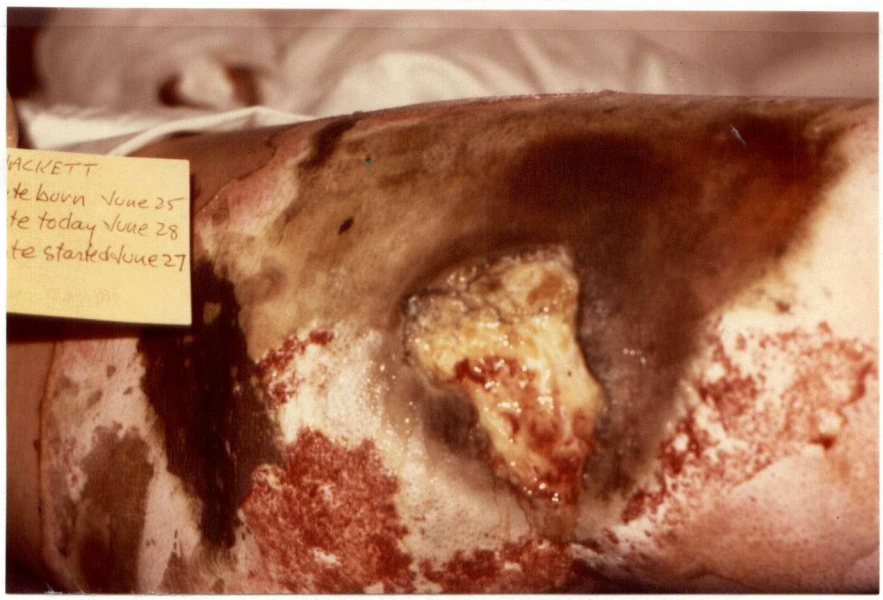

Figure 2

24 hours after therapy begun. Travase applied to lower portion wound only. Anterior wound control under same dressing.

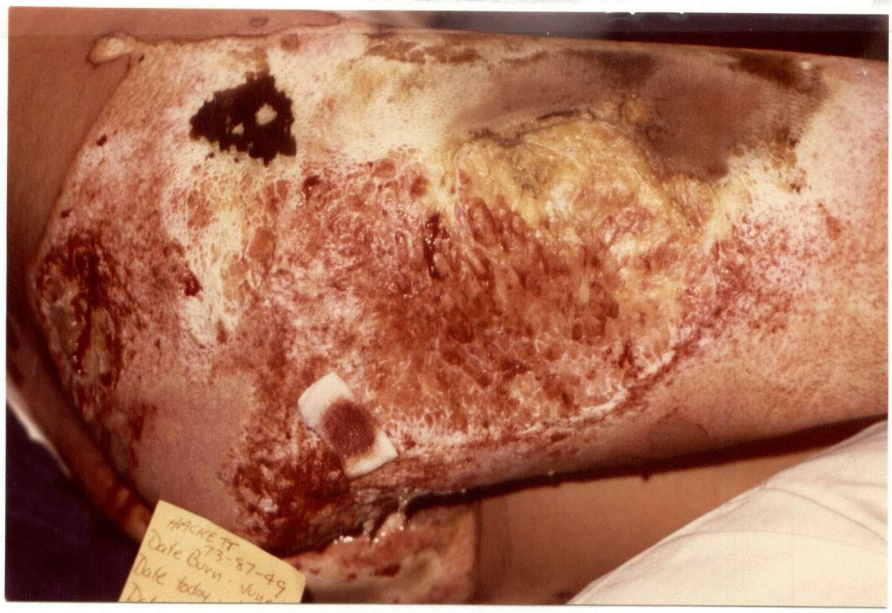

Figure 3

3 days after therapy begun. Complete debridement posterior wound. Anterior wound little debridement.

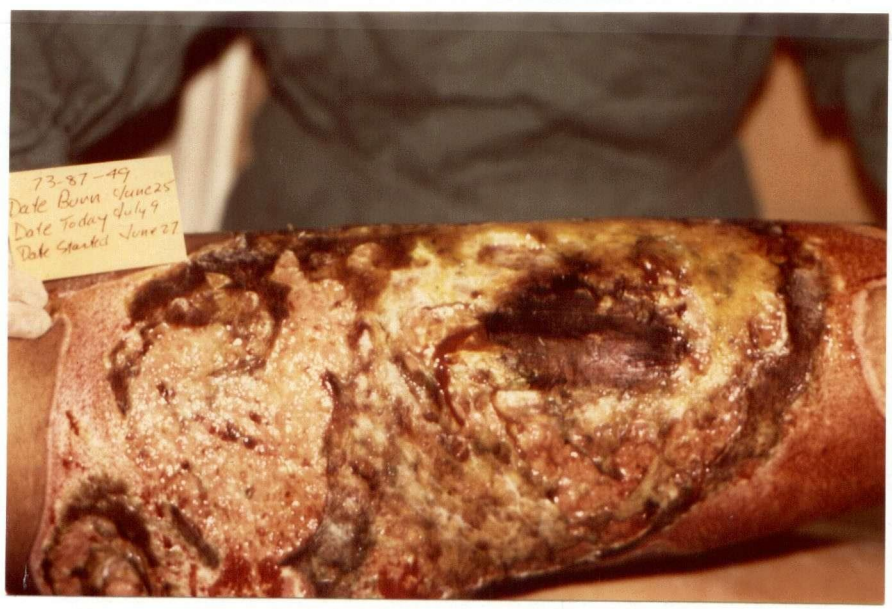

Figure 4

12 days after therapy begun. Still little debridement anterior wound while posterior wound shows evidence of burn wound infection.

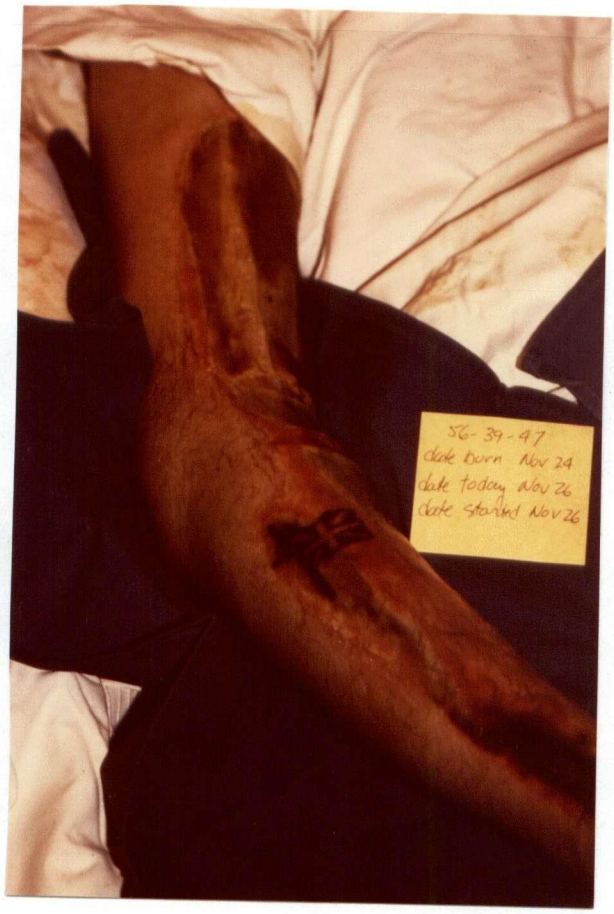

Figure 5

Right arm - 58 year old male with hot metal burn, both arms. 2 days post burn prior to initiation Travase treatment. Note escharotomy of full thickness area.

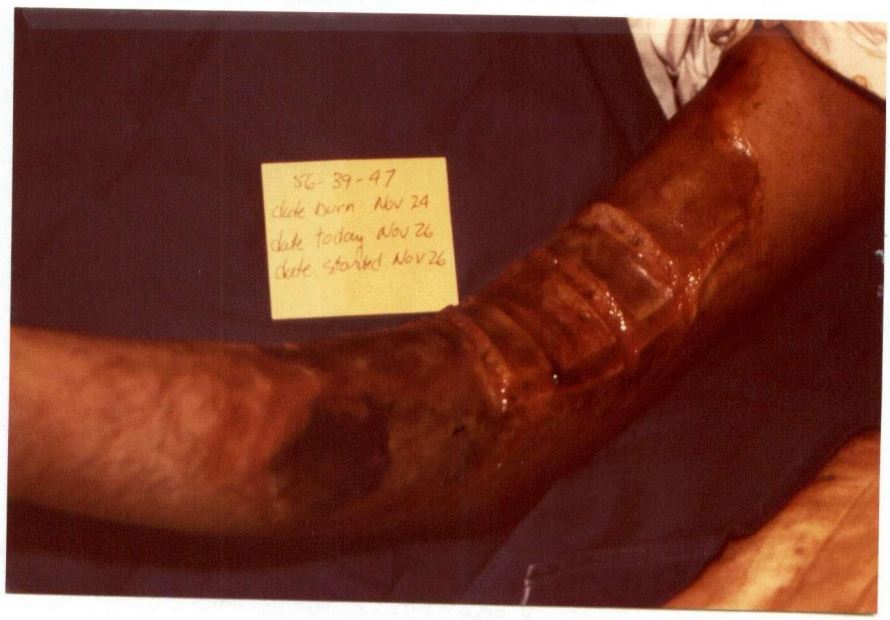

Figure 6

Left arm - Similar burn to Figure 5. Used as control.

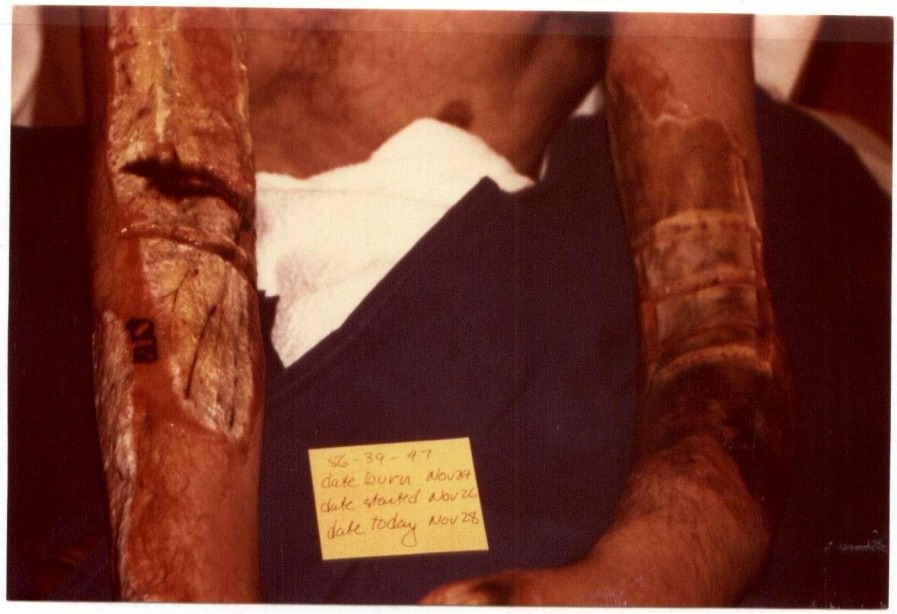

Figure 7

2 days after therapy begun. Note superficial debridement right arm. Left arm unchanged and unable to extend at elbow.

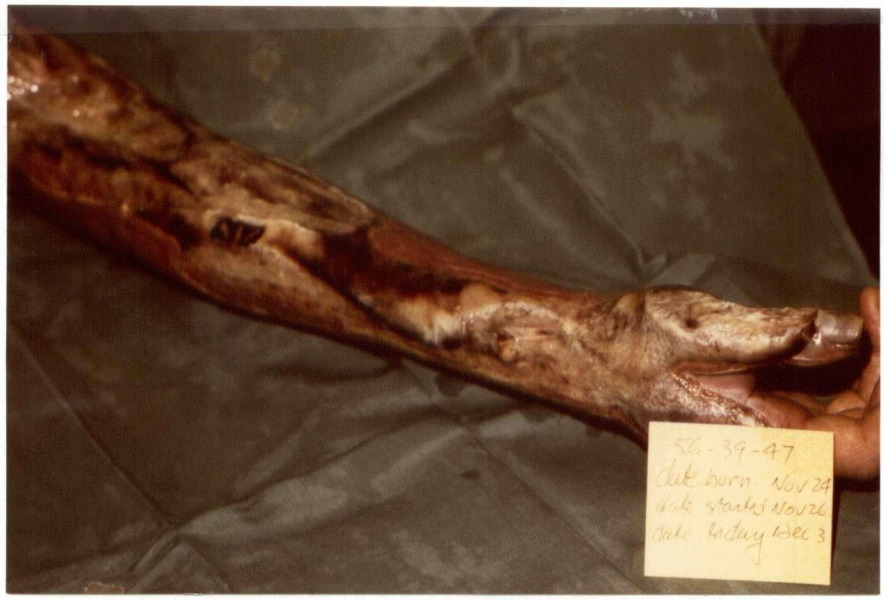

Figure 8

Right arm - 7 days after therapy begun, prior to wound excision. Incomplete debridement and burn wound infection.

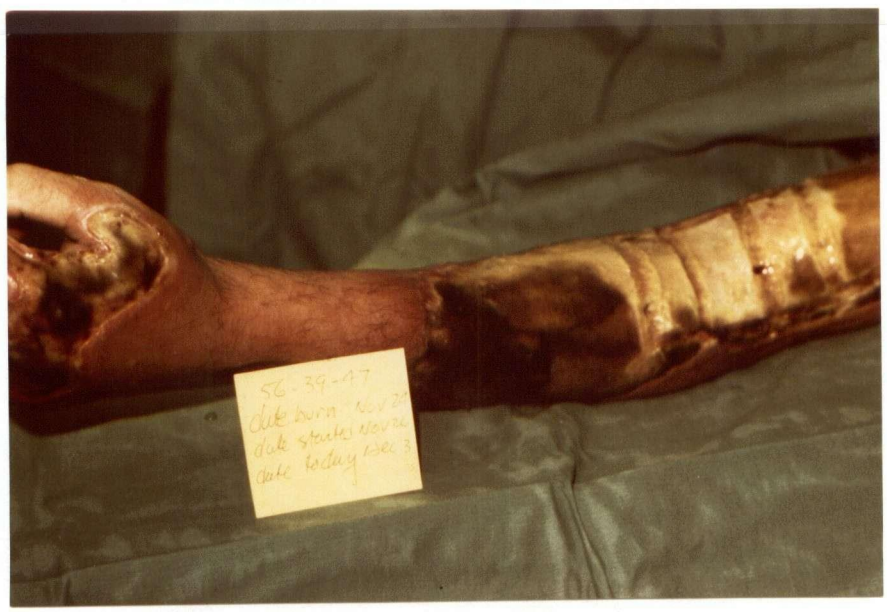

Figure 9

Left arm - Virtually no debridement and burn wound infection.

TABLE VI

COMPLICATIONS

Local Pain on Application of Travase	
None	10
Minor	11
Severe	1
Severe - Discontinued	3
Local Hemorrhage Under Travase Dressing	
None	22
Minor	2
Severe	1
Severe - Discontinued	0
Local and Systemic Sepsis	
None	17
Controlled with antibiotics	4
Discontinued	4

DISCUSSION

Assessment of the clinical worth of enzymatic eschar debridement agents must be made on the basis of in vivo use. Previous in vitro work as outlined above,[13, 17] has demonstrated the superiority of Travase as an active enzymatic agent compared to previous enzymes available. In vivo reports to date,[12, 14] have reported highly favorable results with 70 to 90% satisfactorily debrided and complication rates reported at 8.6% with only a 1.6% discontinuance rate in Garrett's study. Krizek's recent in vitro study[15] suggests the occlusive method of application is responsible for an increased rate of burn wound sepsis and this was confirmed by quantitative bacterial counts in 20 patients. A further recent report by Altemeier, et al.[9] suggests an increased incidence of sepsis with Travase use in their review of 11 patients. Against this background is presented the recent experience at the Vancouver General Hospital.

There is no doubt that, when successful, Travase debrides full thickness burn eschar rapidly and completely, readying the area for grafting. Case 1 exemplifies this, as do figures 1, 2, 3, and 4. With conventional therapy, a full thickness burn, unless surgically excised, is rarely debrided and ready for grafting within three weeks of initial injury. Of the 22 areas with onset of treatment within one week of burning, 13 of 22, or 59% were ready for grafting within two weeks, and 7 of 22, or 32% were ready within one week. Although the numbers are small, we agree with previous reports that the early burn eschar is more rapidly debrided than the more leathery older eschar. As shown in Table V, those burns started on Travase therapy tended to be completed in a shorter interval than those started between 2 and 7 days. Similarly, those started from 2-7 days

debrided faster than those started from 8-14 days post burn.

However, our complication and discontinuance rate are at considerable variance with previous published reports. Pain on application of the enzyme, although highly variable and personality dependent, was most commonly encountered. It resulted in discontinuance of therapy in 3 patients whose wounds, however, subsequently proved to be deep partial thickness. Iced soaks had no demonstrable alleviating effect. Bleeding was not a major problem in our series and no allergy was observed.

Burn wound sepsis with septicemia was the most serious complication encountered and resulted in 4 of our 7 discontinued cases. The sepsis was thought, on clinical grounds, to be caused by the Travase treated area, although the exact source was difficult, if not impossible, to isolate. Of these cases, 4 occurred early in the series prior to the concurrent use of Gentamycin and 4 further episodes occurring later were continued on Travase alternating with the topical antibiotic with control of the sepsis. In addition, our severe septic complications occurred in either very extensive burns, the elderly, or otherwise systemically ill or debilitated patients. In a concurrent series of 108 patients not treated with Travase at the Vancouver General Hospital, 19 of 108, or 17.5% developed sepsis related to the burn wound. These findings of a 33% incidence of clinical sepsis in the burn wounds while on Travase, almost twice the incidence of non-Travase treated patients, contradict the findings of Garrett[12] and Friedman[14] and agree with those of Krizek[15] and Altemeier.[9] The criteria for selection of patients suitable for Travase therapy has now been modified to exclude the above conditions and limit the size of the area treated.

Overall, all but 3 patients had some minor or major complaint or complication of Travase therapy. Some problems can be controlled by analgesics for pain, pressure for bleeding, or antibiotic coverage for sepsis, but a remainder--7 of 25, or 28% in our series--had complications severe enough to warrant discontinuance of therapy.

SUMMARY

From the clinical evaluation of 25 patients to date, Travase has proven to be an effective adjunctive agent in the treatment of burns, but its limitations and potential liabilities have not been sufficiently stressed.

1) Travase must be initiated within seven days of the burn and preferably within 48 hours to have a maximum effect.
2) Pain is much more common than previously reported and is a major source of patient dissatisfaction.
3) Concurrent sepsis when Travase is used alone was more common than previously noted, but may be controlled by concurrent use of a topical antimicrobial. Caution must be used if applied to the elderly, otherwise systemically ill or extensively burned patients.
4) Satisfactory results judged as complete debridement in 14 days from initiation of therapy occurred in 59% of cases begun within one week of burn. These figures will improve with more rigid selection of patients, timing of application, and concurrent use of an antimicrobial, but emphasis must be placed on the fact that Travase is an adjunct to conservative and surgical debridement and not panacea.

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