

## Intravenous Semelil (ANGIPARS™) as a novel therapy for pressure Ulcers: A randomized clinical trial

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### ABSTRACT

The prevalence of pressure ulcers of the foot is a major health care problem in frail elderly patients. A pressure sore dramatically increases the cost of medical and nursing care, and effective treatment has always been an essential nursing concern. Management options for pressure ulcers include local wound care; surgical repair and, more recently, topical application of growth factors.

The main goal of this study was to examine the effects of intravenous treatment of Semelil (ANGIPARS™), a new herbal extract in patients with severe, noninfected pressure ulcers of the foot.

As a randomized clinical trial, 18 patients with pressure ulcers were recruited from Vali-e-Asr hospital, Medical Sciences/ University of Tehran, Iran. Nine patients received intravenous Semelil (ANGIPARS™) besides to conventional therapy and nine received only conventional treatment.

At the baseline, the treatment and control groups did not differ across demographic variables, clinical characteristics, and functional measures. The mean surface areas of the ulcers were reduced  $43.2 \pm 57.4 \text{ cm}^2$  (80.3%) and  $2.8 \pm 6.2 \text{ cm}^2$  (6.3%) in the treatment and control groups, respectively ( $p=0.000$ ).

The average reduction in pressure ulcer area at four weeks was statistically and clinically greater in the treatment group than in the control group. So, intravenous Semelil (ANGIPARS™) can be recommended as an effective treatment for patients with severe pressure ulcers.

**Keywords:** Semelil (ANGIPARS™), Pressure ulcer, Intravenous, Intervention

### INTRODUCTION

Pressure ulcers are one of the major causes of morbidity in older people and the most important care problem in nursing home residents (1,2) and they dramatically increase the cost of medical and nursing care (3). In particular, pressure ulcers of the foot are very common and are difficult to heal among elderly immobilized patients. Pressure ulcers at the malleolus, heel, or both develop as a result of pressure, shear, or friction concentrated on a small area over a bone prominence that lacks subcutaneous tissue. One of the most important parts in estimation of disease load is the disability resulting from the diseases such as injuries due to trauma, car accidents, brain vessel diseases, diabetes and osteoporosis. Induced bedsore in the above mentioned diseases and other reasons causes major problems and disabilities.

In Iran, 5000 patients suffer from spinal cord injury (SCI): of these, 2000 are Iran-Iraq war victims and 3000 are handicapped due to other reason (4). In view of the enormous prevalence of pressure ulcers in war victims and other spinal handicap patients, and the importance of these lesions in terms of morbidity, mortality and cost of treatment, regardless of stage, prompt treatment is essential. An untreated pressure sore may worsen and leads to cellulites, chronic infection, or osteomyelitis. Management options for pressure ulcers include local wound care; surgical repair; and more recently, topical application of growth factors (5-6).

Semelil (ANGIPARS™) is a new herbal extract which have been shown to play an important role in wound healing in previous clinical studies (7). Other basic and toxicology studies showed that

ANGIPAR<sup>TM</sup> has no severe acute or chronic toxicity (8-10) and this herbal extract in intravenous route is more effective than standard therapy without any side effects in diabetic foot ulcers (11-13).

In the present study the efficacy of intravenous ANGIPAR<sup>TM</sup> compared with conventional treatment in patients with pressure ulcers.

### MATERIALS AND METHODS

A randomized controlled trial with four weeks follow-up was performed for patients admitted to Vali-e-Asr hospital, Medical Sciences/ University of Tehran, over a period of one year (August 2006 and August 2007).

All patients with ulcers resulted from spinal inconveniences (accidental or congenital), amputation of the lower limbs, chronic diseases like brain vessel disorders and fractures due to osteoporosis were included in the study. The ulcer size was at least 1 cm<sup>2</sup> (measure of the longest length in longest width) occurring within the last 2 weeks. All patients with acute infection of ulcer or any ulcer with bone exposure were excluded. Other exclusion criteria were: any other disease or situation that impairs ulcer improvement (such as malignancies, vasculitis, diabetes, connective tissue diseases, Immunity system disorders, etc.) alcohol and substance abuse, dialysis and renal failure, corticosteroid consumption, immune suppressive agents, radiotherapy, chemotherapy and any known drug hypersensitivity.

All patients provided written informed consent at enrollment for pre randomization activities and at the initiation of treatment for follow-up activities and treatment.

#### *Study Design and Treatment Protocols*

After patient involvement, primary assessment in addition to evaluation for inclusion and exclusion criteria was performed as followings:

Exact inspection of the ulcer, measurement of its diameters and complete explanation of the ulcer features; photography, mapping and planimetry.

Patients received drugs daily and were evaluated: Daily wound examination before drug administration and renewing the dressing by a physician, Physical examination and taking history from patients, Wound debridement between therapies according to physicians' diagnosis, photography and measurement of the ulcer diameters to assess any improvement, steadiness or regression per two weeks, weekly documentation of patients' compliance, their adherence and side effects recorded and managed. Laboratory assessments were carried out before and at the end of treatment period for serum

hemoglobin level, blood count, and serum glucose level.

Nine patients received intravenous Semelil (ANGIPAR<sup>TM</sup>) and conventional treatment, and nine received only conventional treatment.

For both groups, treatment began in the absence of clinical signs and symptoms of active topical infection. All patients received the same daily local care. Treatment was continued either until the wound healed completely or for a maximum of four weeks.

#### *Treatment Group*

In this group each patient received four mL of ANGIPAR<sup>TM</sup> that was diluted in 100 mL of balanced salt solution, and infused for 30 minutes every other day for four weeks (28 days).

#### *Control Group*

In this group, a balanced salt solution was used as placebo, and wound was dressed with sterile vaseline cover.

## RESULTS

#### *Demographic data*

Eighteen patients were enrolled in the study and no clinically important differences were observed in their demographic or baseline characteristics (Table 1). They had skin ulceration for a mean of two months, without substantial differences between the treatment and control groups. Location of the ulcer was similar between groups. All of the patients continued treatment until completion of the trial and none of them experienced severe adverse consequence related to the treatment.

#### *Efficacy data*

Efficacy was determined by using target ulcer surface area measurements relative to baseline values taken at the start of the trial. The mean relative surface areas were tested for significance during the study period.

Ulcer surface area in intervention group was  $57.2 \pm 76.7$  at the first visit and after completion of the trial decreased to  $20.0 \pm 14.1$  ( $p=0.008$ ). In contrast, ulcer surface area in control group was  $19.5 \pm 16.1$  at the first visit and after completion of the trial decreased to  $16.7 \pm 13.6$  ( $p=0.144$ ). The mean percentages of surface reduction compared to the baseline size among intervention and control groups were:  $80.3 \pm 10.4$  vs.  $6.3 \pm 22.7$ , respectively ( $p=0.000$ ).

All of the ulcers were treated with intravenous Semelil (ANGIPAR<sup>TM</sup>) showed a statistically significant acceleration of the healing process (Table 2) Advancement of epithelial tissue from

**Table 1.** Baseline characteristics of study subjects (mean  $\pm$  SD)

	ANGIPARS™ (n=9)	Control (n=9)	P- value
Age (year)	46 $\pm$ 20.6	46.0 $\pm$ 22.7	0.982
Sex (M/F)	7/2	7/2	1.000
Area of ulcer (cm <sup>2</sup> )	57.2 $\pm$ 76.7	19.5 $\pm$ 16.1	0.446
Number of ulcer	1.3 $\pm$ 0.5	1.2 $\pm$ 0.7	0.882

**Table 2.** Ulcer healing status among Semelil (ANGIPARS™) and control groups

	ANGIPARS™ (n=9)	Control (n=9)	P- value
Decrease in ulcer area (cm <sup>2</sup> )*	43.2 $\pm$ 57.4	2.8 $\pm$ 6.2	0.000
Decrease rate (%)	80.3 $\pm$ 10.4	6.3 $\pm$ 22.7	0.000
Healing†			
> 80%	4 (44.4)	0	
50-80%	5 (55.6)	1 (11.1)	0.0001
20-50%	0	0	
< 20%	0	8 (88.9)	

\*Mean  $\pm$  SD; † Number (%)

the margin toward the center of the ulcer was visible in all patients in the intervention group and the total area was reduced in all ulcers in the intervention group. Moreover, after Semelil (ANGIPARS™) intervention, the lesions in the intervention group showed a marked peripheral scar suggestive of a prompt recovery process. Rate of healing in the intervention group was not related to ulcer severity, patient age, or ulcer location.

The ulcers in the control group, which were treated only with conventional therapy, healed more slowly. It is important to note that none of the patients experienced systemic or local side effects during treatment with Semelil (ANGIPARS™) or conventional therapy.

## DISCUSSION

Pressure ulcers have been associated with increased mortality rates in both acute and long-term care settings. Death has been reported to occur during acute hospitalization in 67% of patients who develop a pressure ulcer compared with 15% of at-risk patients without pressure ulcers. Patients who develop a new pressure ulcer within 6 weeks after hospitalization likely to die three times higher than patients who do not develop a pressure ulcer (14-15).

In long-term care settings, development of a pressure ulcer within 3 months among newly admitted patients has been associated with a 92% mortality rate, compared with a mortality rate of 4% among residents who did not subsequently develop a pressure ulcer (16).

Although no gold standard for prevention or treatment of pressure ulcers has been established, data from clinical trials indicate that specific efforts are worthwhile. Preventive strategies include recognizing risk, decreasing the effects of pressure, assessing nutritional status, avoiding

excessive bed rest, and preserving the integrity of the skin. Treatment principles include assessing the severity of the wound; reducing pressure, friction, and shear forces; optimizing wound care; removing necrotic debris; managing bacterial contamination; and correcting nutritional deficits (17).

Growth factors including transforming growth factors alpha and beta, epidermal growth factor, platelet derived growth factor, fibroblast growth factor, interleukin-1, interleukin-2, and tumor necrosis factor alpha given topically have been demonstrated to mediate the healing process. The concept of acceleration of healing of chronic wounds by using these acute wound factors is attractive. However, in trials in pressure ulcers, platelet derived growth factor failed to produce complete healing (18), although it did shorten the time of closure of wounds, as did basic fibroblast growth factor (19,20). The development of wound healing factors is still in its infancy but shows great promise.

The healing process is characterized by an intricate organization of cellular and molecular interactions. Inflammation and coagulation are essential preliminary processes and are followed by angiogenesis, cell replication, and epithelialization (21). The complex series of events resulting in the repair of coetaneous wounds is modulated at least in part by several polypeptide growth promoters, such as interleukins (interleukin-1, interleukin-6, and interleukin-8), insulin-like growth factor, fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, and nerve growth factor (21-25). Topical treatment of wounds with Semelil (ANGIPARS™) has been studied in human models (26). However, their effectiveness and clinical usefulness are still doubtful. The

results of our randomized, controlled trial indicate that intravenous administration of Semelil (ANGIPARS™) and conventional treatment is more effective than only conventional therapy for patients with severe pressure ulcers. The first sign of wound healing in the treatment group was evident during the second week of treatment and was characterized by the advancement of epithelial tissue from the margin toward the center of the ulcer.

The mechanisms responsible for the efficacy of this herbal extract treatment might be related to stimulation of proliferation of endothelial cell and

vascular neoangiogenesis.

This herbal extract may act indirectly by modulation of inflammation and also acts directly

on endothelial cells and probably plays an important role in angiogenic activity.

The results of this randomized, controlled trial indicate that intravenous application of this herbal extract may be an effective therapy for patients with severe, acute pressure ulcers. However, further studies are warranted for better understanding of the benefit of intravenous Semelil (ANGIPARS™) treatment in patients with chronic skin ulcers.

#### ACKNOWLEDGEMENTS

The authors want to express their appreciation to ParsRoos Co. for supporting this research and for providing ANGIPARS™ and also wish to extend their thanks to Dr. M. Arzaghi for critically reading the manuscript and helpful comments.

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