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*Research Article*

# Brown Spiders' Venom Ulcer Necrosis Local Insulin Micro Doses Therapeutic Essay. Literature Review.

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## Abstract

**Background:** Brown spiders' bites ulcers heal in about 3 months. Intralesional insulin micro multiples doses injections accelerate healing ulcers. In 3,5% of brown spiders' accidents occur hemolysis, intravascular coagulation, renal failure and, in 3%, death. Loxosceles venom transforms sphingomyelin into ceramides. Insulin inhibition by ceramides, may be responsible by necrosis, hemolysis, intravascular coagulation, and thrombosis. Relationship between insulin inhibition and lesion development isn't appreciated in literature about loxoscelism.
**Objectives:** 2-Evaluate healing acceleration by intralesional insulin in cutaneous ulcers by brown spiders´ bites in 13 patients, (between 2015-2023) and it's efficacy preventing serious sequelae. Review diagnosis, physiopathology and therapeutic. Discuss ceramides' relationships with insulin resistance and hemolysis. Demonstrate intralesional insulin multiple micro-dosis injections efficacy as efficient treatment. Exhibit lesions photographic aspects, helping earlier diagnosis and treatment, preventing serious sequelae and death, especially, at distant places from serum therapy hospitals.
**Methods:** 3-Intralesional and perilesional applications sections of multiples 0,01ml of insulin NPH solution with 3/5 UI in 1ml of anesthetic or saline, with variable frequency (Gaspar N.K. 2020) and doxycycline. Photographic control.
**Results:** Healing tendency was observed since first applications. All ulcers healed in less than 36days. Authors refer ulcers healing take more than 90days. No patient required reconstructive surgery. No patient developed hypoglycemia symptoms during treatment.
Study Limitations: Small sampling; control group absence; different evolutionary stages injuries treatment; insulin data related in patient's absence.
**Conclusions:** This method proved to accelerate ulcers healing. It´s necessary to clarify insulin resistance aspects in loxoscelism. Healing necessary sections were wound size related.

**Keywords:** brown spiders' ulcers; necrotic ulcers; venom; ceramides; insulin resistance; wounds difficult to heal; insulin healing induction.

## INTRODUCTION

Found globally Loxosceles genus, includes small araneus, with 1-5cm body length, fine long legs, surviving 1-2 years in 8-43$^{0}$t C, with nocturnal habits, laying about 50 eggs[1-2].
Living in dry, dark, quiet places, caves, under rocks, in temperate and tropical regions. At home, they choose attics, basements, cupboards, drawers, boxes, sheets, furniture, shoes, under papers, dry leaves etc.[2-3]. They survive 50 days with no food or water2. Accidents happened 86% at home[4].
In Brazil, there are 50 species[5]. L. Gaucho, L. intermedia and L. laeta are blamed for most accidents [1;2;6;7]. They were 39.409 between 2017 and 2021 in Brazil, most in south region(53%), mainly in Paraná state[8]. Cutaneous-systemic loxoscelism occurred in Chile, in around 5,5% of 200 accidents[9].
Severity is influenced by geographic region[10], injected venom amount and composition[11-14].
There is no laboratory method capable of diagnosing cutaneous or systemic loxoscelism. Most patients never see the spider. An isothermal amplification of DNA samples obtained from experimentally envenomed rabbit, through colorimetric lamp was related as diagnosis alternative[15].

### Cutaneous Loxoscelism

Bite is painless. After hours or days, the local becomes pale. May appear itching, pain, and bullae[11;16]. Over days, occurs induration, erythema, edema[17]. Central ulcer comes up that can spread gravitationally[18]. Usually single, smaller than 10cm.[19], evolves with a dark sunken necrotic center, with well-defined raised edges, intense inflammatory reaction, without

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typical purulent secretion but with mummified crust and hardened peripheral area[17]. This aspect aids diagnosis[11].
Healing usually takes three months[20-21;17;19;22-23] leaving deep scar that can require excision and grafting[24;16;22].
Mixed inflammatory cell infiltrate, tissue aseptic coagulative necrosis and vasculitis occur after venom injection[25].

**Systemic Loxoscelism**

Suspicion should be high, especially in children with cutaneous ulcer, hemolysis, or coagulopathy. Lesion is frequently misdiagnosed as "cellulitis". May occur pruritus, rash, headache, vomiting, fever, arthralgia[26] and coagulopathy[4;27;22;26]. Hemoglobinuria, acute renal failure, rhabdomyolysis, thrombocytopenia, and jaundice may develop within 1-10 days[26]. Bilirubin (BT) and LDH levels[27;24] had 91% specificity and 94% sensibility in a 275 patient series[28]. In 53.5% of patients, D-dimer levels were increased after 1 week and in 25%, after 2 weeks10. Acute kidney injury [29-31;24;13;32;10], occurred with massive hemolysis noticed in 2 of 81 patients[27].
High serum D-dimer level, by endothelial cell activation and intravascular coagulation, total bilirubin (TB), and LDH levels and leukocytosis with neutrophilia indicate necrosis, systemic involvement[27;24;28;33;10] and patient condition. Coombs' test may be positive[33]. Mortality was 3.5% (2/57 individuals)[33]

**The Venom**

Spider evolution had natural selection and increase in noxiousness[34-36]. L. laeta venom revealing superior activity in Brazil[14].
In 1978, Forrester D. et al [37], demonstrated direct lytic action of phospholipase D (referred to as sphingomyelinase D). Phospholipase D metabolizes sphingomyelin into ceramide and phosphocholine[39-40;36]. Ceramides alter immune functions of NK cells, T CD8+ T cells, activating complement and recruiting polymorphonuclear infiltrate[7;13;36].
Venom is a complex of biological toxins especially phospholipase D, metalloproteases, serineproteases, hialuronidase and Inhibitor Cystine Knot (ICK) peptides[31-32], induces rapid coagulation, capillaries occlusion and necrosis17. Proteomic analysis of Loxosceles gaucho venom showed 12 different phospholipases, Astacin-Metalloprotease(ASM) and insecticidal toxin Sicaritoxin-Lia[38].

**Ceramides and Insulin Resistance**

Ceramides are crucial actors in the development of insulin resistance and type 2 diabetes, and negatively affect mitochondrial respiratory chain, hallmark of type 2 diabetes (T2-D)[56].
The insulin inhibition by ceramides, through the protein kinase mTOR (target of rapamycin) has been evaluated by different authors[45-48;39-40;49-54;36]. In addition, insulin production is impaired by potent proinflammatory lactate hydrogenase overexpression[55;36].
Sphingomyelin and phosphatidylcholines constitute more than 50% of membranous phospholipids, exerting important impact on cell signaling, through their catabolic products, ceramides and glucoceramides[41], controlling growth, differentiation, apoptosis[42-43;31], and immuno-inflammatory events[17;44;10].
Insulin has pivotal role in maintaining mitochondrial proteome abundance and quality by enhancing your biogenesis and preventing proteome degradation. Insulin resistance is characterized by inefficient mitochondrial coupling and excessive production of reactive oxygen species[57-58]. Hypoglycemia impairs fibrinolytic balance, increases pro-inflammatory responses, platelet activation, coagulation biomarkers, and reduces function endothelial mediated by nitric oxide[59].
The venom depletes serum hemolytic complement, clotting factors VIII, IX, XI, and XII, prolongs the activated partial thromboplastin time, induces rapid coagulation, occlusion of capillaries, necrosis[17;60;13].

**Therapy**

The specific treatment is serum therapy, (produced through L intermedia venom) applied until for up to 12h after bite. Pauli I. demonstrated beneficial results reducing the size of necrotic area until 48hs[61]. Adverse reactions are described[62].
Systemic treatment involves aggressive supportive care, wound management, blood transfusions, intravenous fluid replacement and antibiotics.
In a mouse model of systemic loxoscelism, venom-induced kidney failure was abrogated by administration of tetracycline, that reduces kidney damage induced by venom[63], the progression of dermonecrotic lesion, the expression of MMP-2 and the induction of MMP-9[67]. Tetracyclines action on MMPs is thought to be mediated by chelation of structural metals within the enzyme[64]. The strength of tetracycline-metal interaction is dependent on metal ion present. Tetracycline's affinity for different divalent zinc differs and is highly dependent on pH and the presence of other metal ions. Doxycycline action, a zinc dependent enzyme, has a relative superiority over tetracycline and minocycline due to its increased affinity for Zn2+ compared with tetracycline or minocycline[65-66].
Animals, inoculated with venom, treated twice a day for 48 hours with cream containing tetracycline or doxycycline (50 µg/ml) had significant reduction in lesions evolution. Similarly, topical, or oral tetracycline or doxycycline, could control progression of the dermonecrotic lesion in animals injected with venom[67].
The recombinant protein containing β-cell epitopes of different Loxosceles toxins, that generated neutralizing

antibodies in immunized rabbits can be candidate for anti-venom production[68].

Monoclonal antibodies targeting acid SMase inhibitors can be used as therapeutic tools[69].

Imipramine and zoledronic acid capable of reducing acid SMase activity in animals, may be useful in reducing ceramides[70].

Glucocorticoids and immunoglobulins may have benefits treating severe loxoscelism24 and may trigger rapid recovery of platelets[24;10].

Dapsone was used by its activity to reduce polymorphonuclear leukocyte function[11;17] but, should be avoided because it can trigger serious adverse reactions[72-73].

The magnitude of hyperbaric therapy results in necrosis reduction was insignificant[74].

In vitro topic diethilazelat, a plasma membrane fluidizer, with a broad range of immune modulatory activities, inhibit hemolysis cause by the venom and suppressed phospholipase A2 activity in a dose dependent manner[75].

Marbled necrotic skin lesions require surgical removal of the necrotic area[21;11;76;24].

Complications as hyperkalemia (NR≥2.0), metabolic acidosis requiring bicarbonate. Hypotension requiring vasopressors, and hypoxia requiring intubation, occurred only in patients with profound hemolytic anemia[22;26].

## INTRALESIONAL INSULIN THERAPEUTIC ESSAY

### Background

Insulin has metabolic and growth-stimulating actions, both through its own receptors and of its homologous factors (IGFs)[77-80], having pivotal role in mitochondrial proteome preservation[58]. Insulin has been used in humans to recover cutaneous and subcutaneous atrophies[81] and was effective to accelerate healing experimental wounds in Wistar rats. Fibroblasts trans-differentiation in myofibroblasts occurred precociously[82]. Healing acceleration was obtained in difficult healing cutaneous wounds by multiple, simultaneous, intralesional and perilesional injections, of 0.04-0.05UI NPH* mono component insulin, without adverse effects[83].

### Method

a- Multiples micro doses of intralesional and perilesional applications, of 4-5UI of NPH *Novolin Nordisk mono component Insulin NPH 100 UI, diluted in 1ml of lidocaine in multiple simultaneous injections of 0.01 ml (0.04-0.05UI), in various lesions planes and points, repeated at variable time intervals. Debridement of necrotic tissues on the first day treatment.

b- Doxycycline 100mg administration every 12hours in recent cases.

**Patients**

| Pat. | Sex- Age | Days Evolution | Clinical aspects | Insulin sections | Doxicycline | Debridment | Healing/days |
|---|---|---|---|---|---|---|---|
| 1 | M-21 | 136 | 6 cm necrotic dark crust leg ulcer, reaching adipose tissue.(fig1) | 5 | No | Yes | 36 |
| 2 | M-23 | 57 | 2 days after bite, bullae that evolved to 6x8cm. gluteal ulcer with black mummified crust.(fig.2) | 16 | No | No | 40 |
| 3 | M-22 | 126 | 3/4cm left thigh, elevated cyanotic edges ulcer with marble consistence margins. | 4 | No | Yes | 35 |
| 4 | F-52 | 14 | Necrotic, 1,5cm., dry ulcer with raised marble consistence edges, on right breast. | 5 | Yes | | |
| | Yes | 16 | | | | | |
| 5 | F-40 | 6 | Well-defined edges right leg ulceration. (1o episode) | 6 | Yes | Yes | 22 |
| 6 | F-40 | 6 | Right leg ulcer. (2o episode) | 7 | Yes | Yes | 18 |
| 7 | F-40 | 40 | Dry raised indurated edges, 3/5cm., leg ulcer. | 6 | Yes | No | 30 |
| 8 | M-79 | 7 | Erythematous elevated borders, 2/3cm., leg ulcer. | 6 | Yes | Yes | 29 |
| 9 | F-42 | 30 | Necrotic marble consistence, 3x2,5cm., dry crust, raised, irregular edges, ulcer on 2nd finger.(fig-3) | 18 (pos split use) | Yes | Yes | 27 (ankylosis) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 10 | M-67 | 1 | 2mm clear lesion on 12cm. indurated erythematous plaque, that evolved to dark, crust, 1,5cm leg ulcer. | 7 | Yes | Yes | 29 |
| 11 | F-50 | 4 | Erythematous-violaceous plaque, necrosis(4cm.) with raised edges, in right instep. | 9 | Yes | Yes | 23 |
| 12** | F-58 | 13 | 1-day after bite pain, bullae, great induration. After 10days 1.5cm., elevated edges gluteal ulcer and left leg edema (fig.4). | 11 | Yes | Yes | 20 |
| 13 | F-31 | 4 | Pain 4hs after. After 4 days painful erythematous-edematous, 10cm. right tight plaque, with central, 1,7cm., hemorrhagic crust ulcer. | 4 | Yes | No | 8 |
| 14 | F-35 | 8 | A 5cm. gluteal ulceration with erythematous induration. | 7 | Yes | Yes | 30 |

**Figure 1.** Pat.1 (A) First day after "debridment" (leg ulcer with well-defined raise edges) and insulin micro doses treatment. (B) After 5 insulin micro doses injection, healing with good cicatricial aspect.

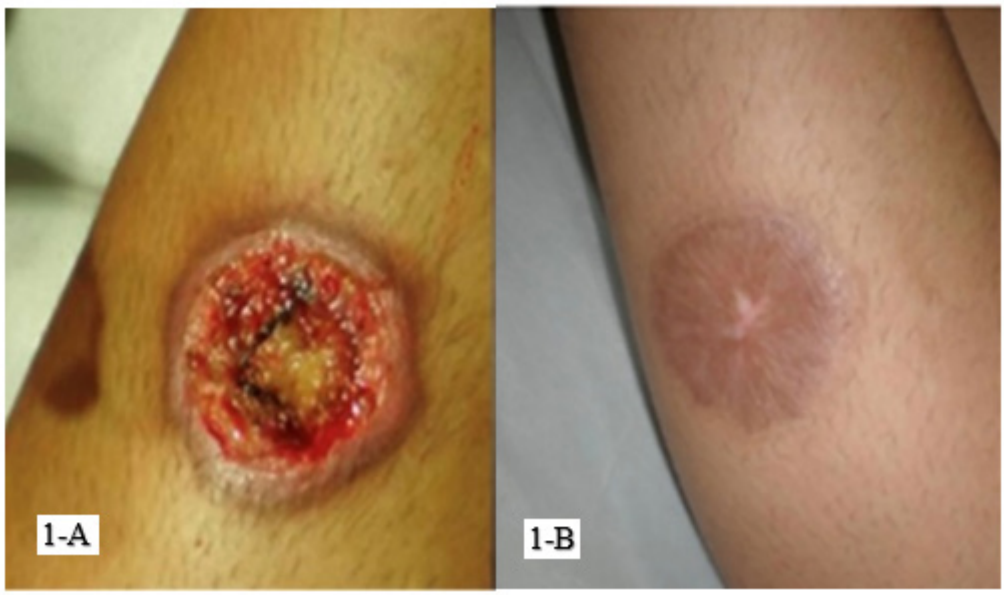


**Figure 2.** Pat.2 (A) Two days after bite, gluteal ulcer with black, mummified, 6x8cm. crust and elevated borders. First day micro doses insulin treatment at lesion edges. (B) Fiftieth six day, after 11th day insulin treatment and 1rst peripheral "debridment". (C) After 18th insulin microdoses injections on the 122th evolution day. (D) Five years later without hipertrofic scar.




**Figure 3.** Pat.9 (A and B) First day treatment. (A) Necrotic ulcer with mummified crust, that spread gravitationally18. (B) After "debridment" and insulin treatment. (C) Thirty days after, was proceeded a surgical incision on the 2nd finger and immobilization with a splint, on extension, during insulin treatment, permitting anatomic position healing, in order to reduce the ankyloses. (D) Forty tree days after insulin treatment, occurs cicatricial ankyloses with minimal defect and perfect function.



**Figure 4.**Pat.12 (A) One day after spider bite and 1rst day insulin multiple micro doses treatment. (B) Eight days of daily insulin micro doses injections. (C) Twentieth day of insulin micro doses treatment when ulcer healing occurs.

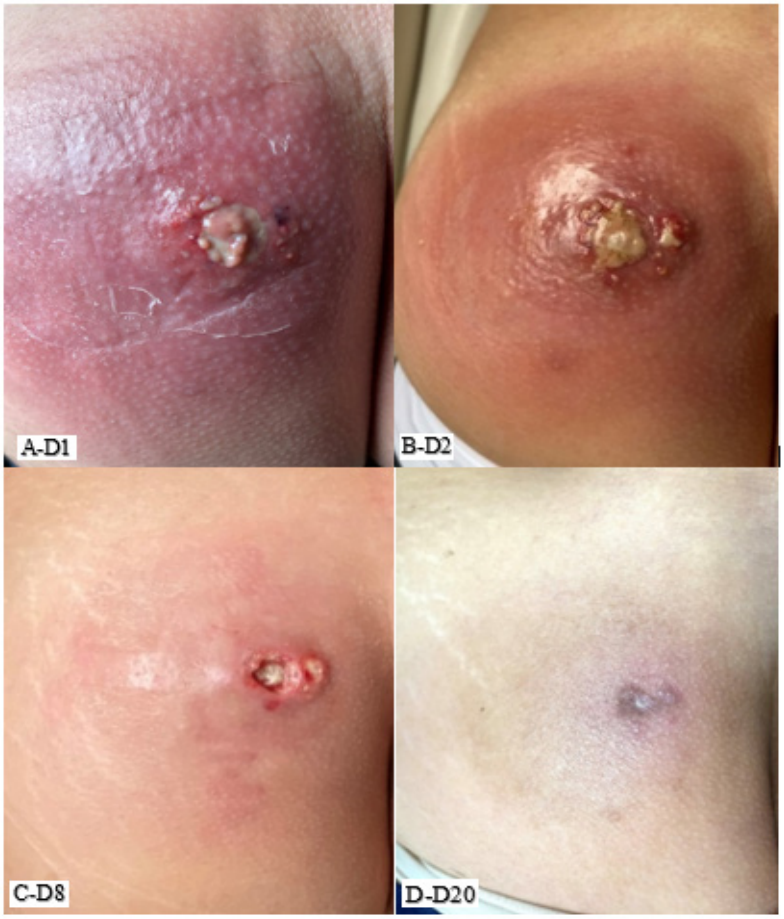
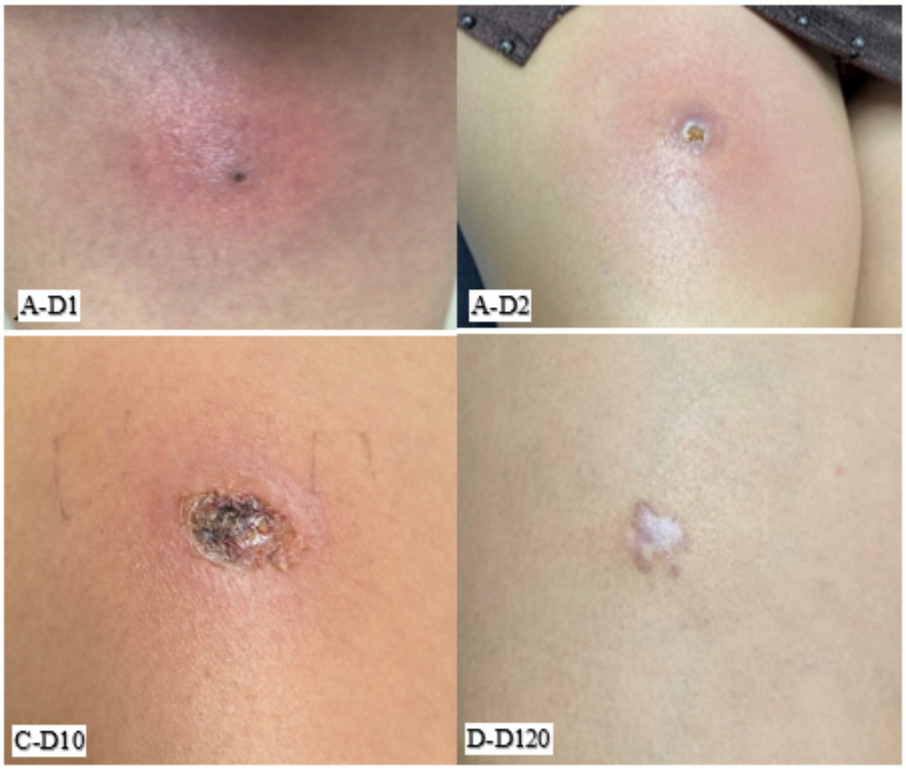



**Figure 5.**Pat.13 (A) Forth day after bite and 1rst insulin micro doses treatment. Lesion with remarkable target aspect. (B) Second day insulin micro doses injection with pale halo (C) Tenth day after bite with crust and 4th insulin application. (D) Four months later, cicatricial aspect after abandoning treatment at 4th section.



## COMMENTS

1- Systemic suspicious loxoscelism should be high, especially in children and younger adults, who presents cutaneous ulcer, hemolysis and coagulopathy.
2- The edges sharply defined and elevated, without purulent secretion aid diagnosis.
3- Debridement of necrotic lesions can accelerate healing.
4- Tetracyclines, especially doxycycline, given early, can limit the aggressive proteases. Topical applications may offer advantages, especially in infants67.
5- The only case taking more than 30days to heal, was n.2, who presented enormous crust that wasn't debrided. In all our cases, cosmetics' cicatricial aspects were good.
6- In case n.9, after occurs cicatricial ankylosis, was proceeded a surgical incision on the 2nd finger and immobilization with a splint, on extension, during insulin treatment, permitting anatomic position healing, in order to reduce the ankyloses with minimal defect and perfect function.
7- Healing time and applications number were related to lesions size and severity. Patients 1 and 3 with long intervals between applications, could have achieved faster healing.
9- The speed and time of wound resolution was dependent on the frequency and number of sessions.

## CONCLUSION

1-Healing ulcers by Loxoscelles venom takes 3 months. With insulin in intralesional micro multiple doses, healing occurs in about 1 month.
2-Healing response onset begins in 24-48 hours, with final resolution in less than 1 month in our patients, indicating that this therapy may help.
3-Different intervals between applications did not change the results.
4-The method proved to be effective and without adverse effects.
5-Regenerative activity onset in all lesions was observed between 1 or 2 days after first application, and can be attributed to its stimulating healing activity, as demonstrated by Gaspar and Gaspar, and the insulin's reduction of ceramides' resistance.
6-Advantages obtained indicate that the process can be successfully used to accelerate healing of brown spider's bites ulcers.
7-According to previous experience (Gaspar 2020)83, applications performed using this method don't determine glycemic changes in adult patients.
8-Raw (or open) wounds can heal with undiluted insulin in topical applications83.
9-Despite a significant correlation between sphingolipids, mitochondrial dysfunction, insulin resistance and T2 D, this subject hasn't received much attention compared to direct sphingolipids effect on insulin signaling pathway84.
10-Insulin's availability and safety use, indicates the method as an effective therapeutic option for difficult-to-heal wounds, without adverse effects.

### Conflicts of Interest

None declared.

### Authors' contributions

Neide Kalil Gaspar: The study concept and design, writing of the manuscript or critical review of important intellectual content, data collection, effective participation in the research guidance, intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases, critical review of the literature, approval of the final version of the manuscript. Marilia Nunes Nogueira: Data collection, or analysis and interpretation of data, writing of the manuscript or critical review of important intellectual content, data collection, analysis and interpretation, effective participation in the research guidance, intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases, critical review of the literature, approval of the final version of the manuscript.

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