REVIEW ARTICLE
doi: 10.35366/112925

Cirujano General
July-September 2023
Vol. 45, no. 3 / p. 160-174

Surgical versus medical management in cutaneous loxoscelism: systematic review and update

Manejo quirúrgico versus tratamiento médico en loxoscelismo cutáneo: revisión sistemática y actualización

Aldo Israel Olan-De Los Santos,[*] Hilda Alejandra Manzo-Castrejón,[‡] Enrique Corona-Díaz,[§] Grecia Fernanda Hurtado-Miranda,[*] Leonel Eduardo Franco-Ponce,[*] Juan Daniel Arreola-Pérez,[¶] Uriel Esaid Arellano-Romero,[*] Juan Manuel Alanís-Nava,[*] Jonathan Javier Ortiz-Márquez,[*] Iván San Pedro-Rodríguez[¶]

Keywords:
loxoscelism, loxosceles, brown recluse spider, treatment, systematic review.

Palabras clave:
loxoscelismo, loxosceles, araña reclusa marrón, tratamiento, revisión sistemática.

[*] Third-year resident of General Surgery, Hospital General Tacuba, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City.
[‡] Attending physician, Plastic and Reconstructive Surgery, Hospital General Tacuba, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City.
[§] First-year resident of Internal Medicine, Centro Médico Nacional La Raza, Instituto Mexicano del Seguro Social, Mexico City.

ABSTRACT

Background and objective: to perform a systematic review on the management of cutaneous loxoscelism to analyze the effectiveness of current therapies in managing this pathology by comparing the effectiveness of medical and surgical management. **Methods:** through systematic search in different databases, we carried out a compilation and synthesis using the PRISMA method for those studies that evaluate a therapeutic intervention; we discarded those that do not make any reference to the validation of a therapeutic strategy for the bite of a spider by the genus *Loxosceles*. **Results:** nineteen studies, including six randomized clinical trials, three non-randomized clinical trials, two cohorts, two systematic reviews, and six case series were chosen. In areas of necrosis greater than 1 cm, surgical excision within the first week to 10 days after the bite is ideal, with significant complications described in less than 48 hours, a protocol with decompressive fasciotomies, necrosectomies, and subsequent coverage with flaps and grafts should be applied for the prevention of compartment syndromes. Pretreatment with dapsone for 14 days reduced the incidence of surgical wound complications compared to chlorphenamine. Hyperbaric oxygen (HBO) therapy at 2.5 atmospheres significantly reduced wound diameter at ten days, even two to three months after the failure of other treatments; however, it did not differ significantly concerning lesion size compared to other treatments. The anti-loxosceles serum reports less probability of developing necrosis and resolution in 97% of the cases. **Conclusions:** there is a period in which the surgical approach benefits patients, after the first 48 hours and before ten weeks. Medical therapy seems to have more evidence for using dapsone and anti-loxosceles serum to avoid the progression

RESUMEN

Antecedentes y objetivo: *realizar una revisión sistemática acerca del manejo del loxoscelismo cutáneo para analizar la efectividad de las terapias actuales sobre el manejo de esta patología con la comparación de la efectividad del manejo médico y quirúrgico.* ***Métodos:*** *a través de las búsquedas en diferentes bases de datos de manera sistemática se llevó a cabo una recopilación y síntesis por medio del método PRISMA para aquellos estudios que evalúan una intervención terapéutica, descartamos aquellos que no hacen alguna referencia a la validación de una estrategia terapéutica para la mordedura de una araña por el género Loxosceles.* ***Resultados:*** *diecinueve estudios, entre ellos seis ensayos clínicos aleatorizados, tres ensayos clínicos no aleatorizados, dos cohortes, dos revisiones sistemáticas y seis series de casos. En áreas de necrosis mayores a 1 cm la extirpación quirúrgica dentro de la primera semana a 10 días después de la mordedura es lo ideal, con mayores complicaciones descritas en un periodo menor a 48 horas, se debe aplicar un protocolo con fasciotomías descompresivas, necrosectomías y posteriores coberturas con colgajos e injertos para la prevención de síndromes compartimentales. El pretratamiento con dapsona por 14 días redujo la incidencia de complicaciones de la herida quirúrgica, al compararla con clorfenamina. El oxígeno hiperbárico (HBO) a 2.5 atmosferas reduce significativamente el diámetro de la herida a los 10 días, incluso dos a tres meses después del fracaso de otros tratamientos; sin embargo, no difiriere significativamente con respecto al tamaño de la lesión en comparación con otros tratamientos. El suero anti-loxosceles reporta menor probabilidad de desarrollar necrosis y resolución en 97% de los casos.* ***Conclusiones:*** *parece existir un periodo*

How to cite: Olan-De Los Santos AI, Manzo-Castrejón HA, Corona-Díaz E, Hurtado-Miranda GF, Franco-Ponce LE, Arreola-Pérez JD, et al. Surgical versus medical management in cutaneous loxoscelism: systematic review and update. Cir Gen. 2023; 45 (3): 160-174. https://dx.doi.org/10.35366/112925

¶ Second-year resident of General Surgery, Hospital General Tacuba, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City.

Received: 04/10/2023
Accepted: 06/28/2023

of cutaneous lesions; in general, few conclusive studies allow establishing therapeutic indications.

en el que el abordaje quirúrgico resulta benéfico en los pacientes y éste se encuentra después de las primeras 48 horas y antes de las 10 semanas. La terapia médica parece tener mayor evidencia al uso de la dapsona y el suero anti-loxosceles para evitar la progresión de las lesiones cutáneas, de forma general existen pocos estudios contundentes que permitan establecer indicaciones terapéuticas.

INTRODUCTION

Justification and objectives: the number of clinical research studies on this subject is continuously increasing; therefore, we undertook the task of synthesizing in an orderly manner and under scientific criteria the existing information to date in order to develop a consensus on the management of loxosceles spider bite; however, there are several limitations: for example, most of them are elaborated with a low level of evidence and degree of recommendation, there are few controlled clinical trials or with a reliable methodological design to give clinical recommendations on the effectiveness of medical versus surgical management for cutaneous loxoscelism in humans for its applicability in daily clinical practice.

The brown recluse spider, also known as the fiddler spider, belongs to the genus *Loxosceles*.[1] Despite more than 42,000 spider species in the world,[2] only a few can produce severe cases of poisoning in humans,[3] among them 33 species of Loxosceles in Mexico.[4,5] Their bite produces loxoscelism, derived from the venom with hemolytic, vasculitic, and coagulant necrotizing characteristics;[6] it causes clinical conditions that may present as localized cutaneous loxoscelism or systemic loxoscelism, less frequently and more severe.[7] The first symptoms in the cutaneous picture start with pruritus and erythema, progressing to severe pain and evolving into a more severe dermonecrotic form[8] *(Figures 1-3)*. Early diagnosis of loxoscelism, usually made by anamnesis and clinical findings, together with a multidisciplinary approach, can save a life or limb and prevent more severe conditions. Several treatments have been described; however, it is still controversial due to the insufficient quality of the available evidence for developing a therapeutic consensus, and there needs to be a standardized treatment approach.[9] Current literature on brown spider bites suggests anti-loxosceles serum, analgesia, antibiotic therapy, dapsone, antihistamines, ice, compression, elevation, hyperbaric oxygen therapy and local management with surgical debridement, and repeated healing of the lesion with or without application of skin graft. Therefore, knowledge of the morphological characteristics, habitat, and severity of the clinical picture caused by the toxicity of the poisons inoculated by each species is essential when distinguishing the severity of each event and deciding the corresponding therapy.[10]

MATERIAL AND METHODS

We elaborated this review through a systematic process that consisted of researching and critically reading the clinical studies with the highest methodological quality by searching different databases and search engines, including PubMed/Medline, UptoDate, Cochrane, Web of Science, Science Direct, among others; using a different combination of words such as "loxoscelism," "loxosceles," or "*brown recluse spider*"; subsequently, the search was supplemented with additional search engines such as Wiley online library, Ovid, Scielo and Google academic, and adding a new search word of "*arachnidism*." The search of the different sources of information consulted was performed with no publication date limit until March 2023. For eligibility, we chose a bibliography without language distinction,

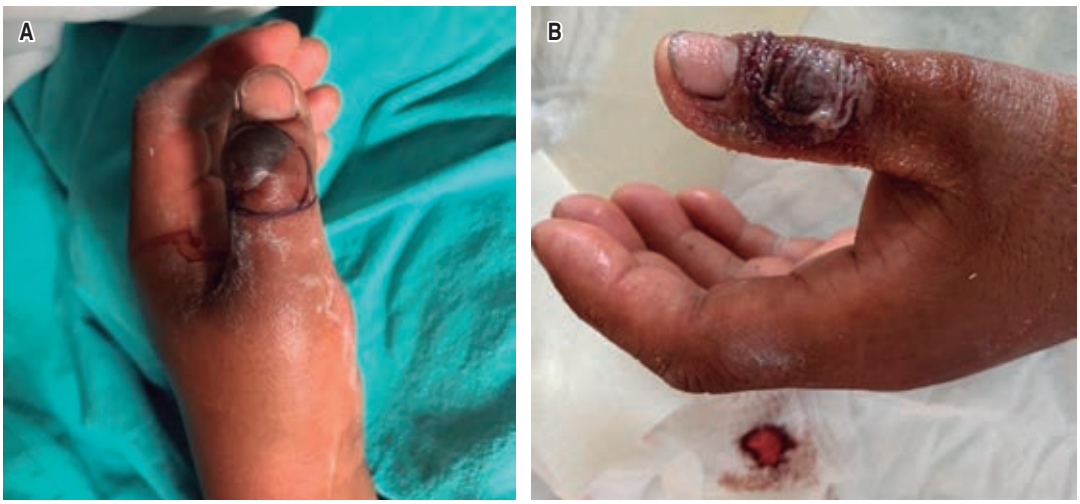

Figure 1: *38-year-old male patient with a loxosceles spider bite, 12 hours of evolution with a livedoid plaque and necrosis area involving subcutaneous cellular tissue.* ***A)*** *Livedoid plaque on the dorsum of the thumb secondary to a loxosceles spider bite. Congestive areas and ecchymosis secondary to vasoconstriction and ischemia caused by the venom are seen in the periphery of the wound.* ***B)*** *A lesion with local ampules without systemic manifestations is observed after local and symptomatic management.*

Figure 2: *Dermonecrotic skin lesion due to probable loxoscelism.*

including papers in Spanish, English, French, and Portuguese. Those explicitly mentioning a therapeutic intervention in the title or abstract were included to evaluate the full-text systematic review; we discarded those that did not reference the validation of a therapeutic strategy for the bite of a spider of the genus *Loxosceles*. Details of the results of the different search engines, description, and selection of the articles are described in *Table 1*.

Analysis of the studies

The distribution of articles initially evaluated for review of titles and abstracts, as well as those selected for full-text analysis. Those studies finally included to carry out the systematic review, which was done by using the PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses),[11] which consists of the critical analysis of each phase of the elaboration and is summarized in *Figure 4*. The study selection and information extraction methodology comprised the studies' identification, review, eligibility, and inclusion. The identification process was carried out through the records identified by searching the databases above, carried out by all the authors of this review blindly and independently from August 2022 to April 2023, obtaining 22,318 records, among which those that in the title mentioned

other arachnids such as bites by the genus *Latrodectus* (black widow), tarantula, scorpion sting or snake bite were excluded. Only those that mentioned a spider of the genus *Loxosceles* in the title were included. We obtained 5,162 references for analysis of titles and abstracts after eliminating duplicates through searches in the different sources of information cited, of which 175 were selected for full-text analysis. From this total of studies, and in order to evaluate the risk of bias of the included articles, the authors were given the

Figure 3:

Progression of a loxoscelism skin lesion when the patient herself manually manipulated the necrotic eschar.

Table 1: Databases, search engines, and keywords used, and results.

PubMed/Medline	Up to Date	Cochrane
Loxoscelism: 45 Brown recluse spider: 371 Loxoscelism: 740 Loxosceles: 740 Arachnidism: 1,560	Loxoscelism: 3 Brown recluse spider: 10 Loxoscelism: 3 Loxosceles: 3 Arachnidism: 2	Loxoscelism: 0 Brown recluse spider: 5 Loxoscelism: 4 Loxosceles: 4 Arachnidism: 13
Wiley online library	**Web of Science**	**Science Direct**
Loxoscelism: 0 Brown recluse spider: 356 Loxoscelism: 120 Loxosceles: 352 Arachnidism: 4,210	Loxoscelism: 2 Brown recluse spider: 429 Loxoscelism: 343 Loxosceles: 752 Arachnidism: 232	Loxoscelism: 33 Brown recluse spider: 1,187 Loxoscelism: 543 Loxosceles: 1,442 Arachnidism: 5,907
SciELO	**OVID**	**Academic Google**
Loxoscelism: 52 Brown recluse spider: 8 Loxoscelism: 63 Loxosceles: 92 Arachnidism: 14	Loxoscelism: 5 Brown recluse spider: 688 Loxoscelism: 478 Loxosceles: 946 Arachnidism: 270	Loxoscelism: 1,110 Brown recluse spider: 9,140 Loxoscelism: 2,220 Loxosceles: 7,970 Arachnidism: 1,980

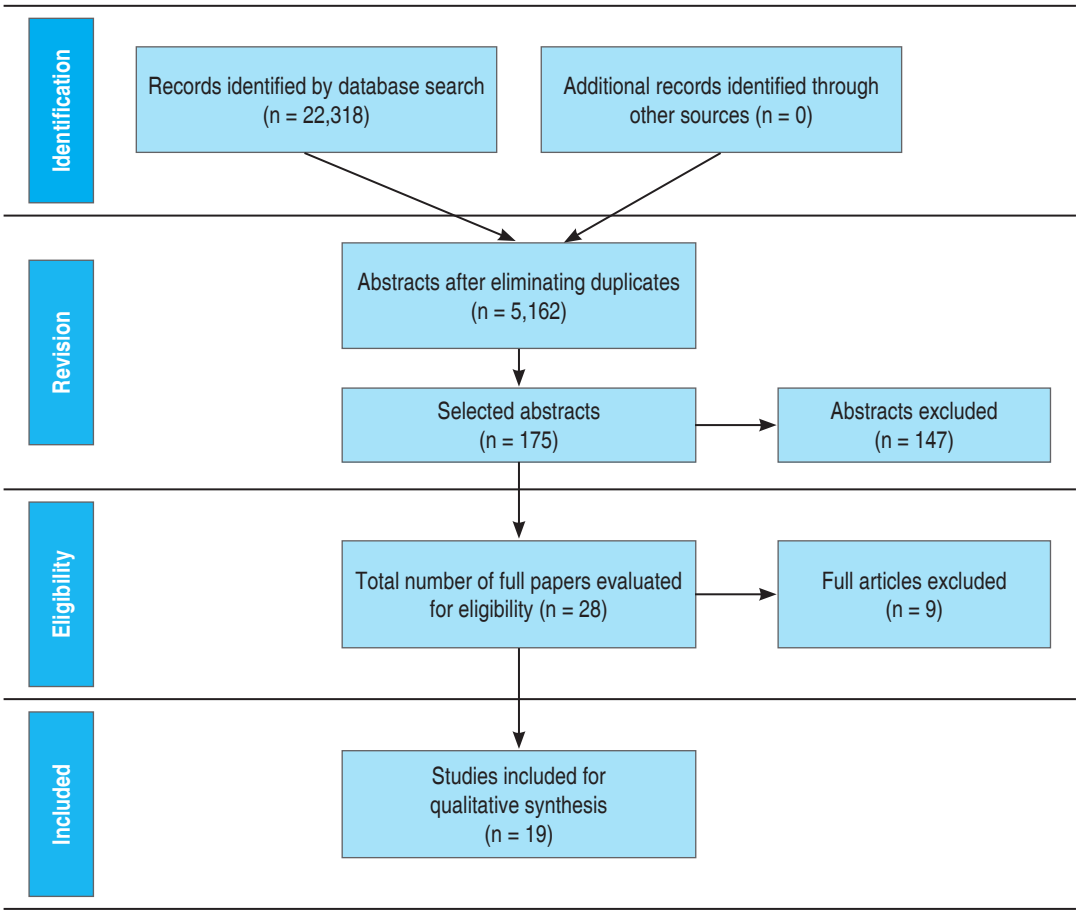

Figure 4:

The PRISMA method.

task of classifying them according to the level of evidence, degrees of recommendation, and methodological quality based on the scale recommended by the National Health and Medical Research Council (NHMRC),[12] in which each author classified studies, and the independent classification of each author was subsequently submitted to peer review with one of the authors (OSAI). The articles searched and classified are summarized in *Table 2*. Only 28 full articles were evaluated for eligibility; a peer review was conducted between one of the authors (OSAI) and each of the other authors to determine the studies included for qualitative synthesis. Data extraction was performed independently by each of the reports and publications authors.

To carry out this systematic review, we began the elaboration of the protocol, describing the specific research question, for which we used the acronym PICO[13] for the construction of the question:

P. *Study population:* the characteristics of interest of this study include a population of animals and humans of any age affected by the bite of a spider of the genus *Loxosceles*.

I. *Intervention to be evaluated: Table 3* compares the interventions such as anti-loxosceles serum, dapsone, chlorphenamine, hyperbaric oxygen, surgical treatment, negative pressure, nanocrystalline silver, cyproheptadine, topical nitroglycerin, and vitamin C.

C. *Comparison of intervention:* The effectiveness of current medical therapies proposed for managing loxoscelism and the application of timely early surgical management are compared.

Table 2: Identification and review of the study selection and classification process by author.

Author	Full-text articles	Classified articles
Alanís Nava, JM	5	15
Arellano Romero, UE	1	25
Arreola Pérez, JD	2	25
Corona Días, E	25	10
Franco Ponce, LE	45	1
Hurtado Miranda, GF	10	15
Olán de los Santos, AI	74	38
Ortiz Márquez, JJ	11	15
San Pedro Rodríguez, I	1	31
Total	**175**	**175**

O. *Outcomes:* the results of the effect of the intervention will be presented, evaluating the complete cure of the condition, the presentation of sequelae, adverse effects, or treatment failure.

The exclusion criteria for the full-text studies evaluated for eligibility were isolated case reports, reviews, observational or descriptive studies, letters to the editor, and case series without analysis of treatment effectiveness.

The inclusion criteria for the studies selected for the qualitative synthesis were randomized and non-randomized clinical trials, and case series with analysis of treatment effectiveness, systematic reviews, and cohorts.

RESULTS

The search and selection processes followed the PRISMA 2020 flow chart adapted by Boers,[14] Mayo-Wilson and collaborators,[15] and Stovold and associates.[16] From 22,318 records obtained through all databases. After eliminating duplicates, 5,162 references were obtained for title and abstract analysis, of which 175 were selected for full-text analysis. Only 28 full-text articles were evaluated for eligibility; by applying exclusion criteria, 19 studies were included in this review. Of these, six were randomized clinical trials, three were non-randomized clinical trials, two were qualitative systematic reviews (without meta-analysis), two were cohorts, and six were case series, which evaluated the effectiveness of the application of anti-loxosceles serum, dapsone, chlorphenamine, hyperbaric oxygen, surgical treatment, negative pressure, nanocrystalline silver and cyproheptadine *(Tables 4 and 5)*. The nine studies that met the inclusion criteria by evaluating new therapeutic strategies for loxosceles were finally excluded because they were isolated descriptive case reports on the evolution in single individuals or did not compare the safety and efficacy of the proposed treatment with any intervention already described.

Summary of results

Surgical management

Auer et al.[17] were among the first to report the importance of surgical intervention in the management of loxosceles spider bites in a non-randomized clinical trial; surgical management was classified into three groups: early incision < 10 days after the bite with closure in a second surgical time by suture or graft, late incision three to ten weeks after the bite, and closure in a single surgical time. Ten days after the

Table 3: Interventions evaluated in the systematic review.

Dapsone (diamino diphenyl sulfone)
Chlorphenamine
Anti-loxosceles serum
Hyperbaric oxygen
Surgical management: early or late excision, decompressive fasciotomies, necrosectomies, and posterior coverage (flaps and grafts)
Negative pressure
Nanocrystalline silver
Cyproheptadine
Topical nitroglycerin
Vitamin C

Table 4: Description of the interventions of each study chosen with the results and outcomes obtained.

Study	Population (n)	Intervention	Outcomes
Auer Arthur I[17]	33	• Early incision: <10 days + second-time closure with suture or grafting • Late incision: 3-10 weeks + closure • Late incision: 3-11 weeks + grafting	Cure, in most cases, 1 infection, 1 graft slippage with partial loss Cure in most cases, 1 late infection 4 graft losses, 2 unsuccessful closures, 1 phlebitis
Rees Riley S[18]	31	• Early surgical excision < 48 hours • Dapsone + late surgical excision	6 cases of late healing, 3 infections, 1 ulnar nerve entrapment 3 complete cures, 4 resolutions in 2 weeks, 2 in 3 weeks, 1 infection, 2 cellulitis. 3 nodulation
Staneff John[19]	7	Decompressive fasciotomies, necrosectomy, flap or grafting	Clinical recovery of patients in an average of 11 days
Maguiña Ciro[20]	39	• Dapsone 100 mg • Chlorphenamine 4 mg	Favorable outcome in 18 of 20 patients Favorable outcome in 10 of 19 patients
Maguiña Ciro[21]	39	• Dapsone 100 mg • Chlorphenamine 4 mg	Infected ulcers treated with clindamycin 300 mg
Rees Riley S.[22]	16	• Dapsone 250 mg • Anti-loxosceles serum 2 mg/mL • Dapsone + Anti-loxosceles serum	Healed in 20 ± 2 days, 2 cutaneous necroses in large ulcers
Borrasca-Fernandes Carla[23]	8	Anti-loxosceles serum 46 hours post-bite	Complete healing between 34 and 98 days in 6 patients
Malaque Ceila MS[24]	146	• 74 cases with anti-loxosceles serum • 72 cases without anti-loxosceles serum	Lower probability of developing necrosis Seven early adverse reactions, 4 early adverse reactions, 3 local infection
Isbister Geoffrey K[25]	75	Anti-loxosceles serum	Complete response in 97%. 2 early allergic reactions and 1 case of serum sickness
Manriquez Juan J[26]	–	Dapsone, surgical treatment, chlorphenamine, anti-loxosceles serum	–
Hobbs Gregory D[27]	32	• Hyperbaric Oxygen At 2 atm for 2 hours • Dapsone 50 mg • HOB + dapsone	Reduction of induration at days 7 and 14 in treatment with dapsone
Phillips Scott[28]	–	• Hyperbaric oxygen at 2.5 atmospheres • Dapsone 1.1 mg/kg • Cyproheptadine 0.125 mg/kg	Decrease in the total size of the lesion
Maynor M. L[29]	41	• Without hyperbaric oxygen • Hyperbaric oxygen at 2.5 atmospheres with O_2 100% • Normoxic hyperbaric oxygen	Significant reduction in wound size at 10 days with 2.5 atmospheres with O_2 100%.
Hadanny Amir[30]	3	Hyperbaric oxygen 2 -3 months later	Full resolution
Del Puerto Constanta[31]	17	Intravenous antibiotics, systemic corticosteroids, dapsone, dapsone, etc.	Complete resolution in 50% with corticosteroids and dapsone Complete resolution in 3 patients on steroids
Mold James W[32]	262	Corticosteroids, dapsone, topical nitroglycerin, and vitamin C	Slower healing with corticosteroids and dapsone Increased probability of healing with dapsone
Schenone H[33]	216	Antihistamines, injectable corticosteroids, anti-loxosceles serum	Local control at 12 noon
Wong S. Lindsey[34]	8	Negative pressure (vacuum-assisted closure)	Healing of all wounds
Chrysostomou D[35]	11	Topical nanocrystalline silver	8 complete healings in one week, 3 wounds sloughed

Table 5: Summary of the studies included for the qualitative review with methodology used and methodological quality.

Main author	Title	Level of evidence	Grade of recommendation	Type of study	Intervention
Auer Arthur I.[17]	Surgery for necrotic bites of the brown spider	III-1	C	Non-randomized clinical trial	Surgical treatment*
Rees Riley S.[18]	Brown recluse spider bites. A comparison of early surgical excision versus dapsone and delayed surgical excision	III-1	C	Non-randomized clinical trial	Surgical treatment* vs. dapsone
Staneff John[19]	Presentation of an effective protocol for the treatment of myodermonecrolysis due to cutaneous loxoscelism	IV	D	Case series	Surgical treatment
Maguiña Ciro[20]	Dapsone (DDS) in cutaneous loxoscelism	II	B	Randomized clinical trial	DDS (phyaminodiphenyl-sulfone) vs chlorpheniramine
Maguiña Ciro[21]	New therapeutic schemes in cutaneous loxoscelism in Lima, Peru	II	B	Randomized clinical trial	Dapsone (DDS) vs chlorphenamine
Rees Riley S.[22]	The diagnosis and treatment of brown recluse spider bites	II	B	Randomized clinical trial	Dapsone vs. anti-loxosceles serum
Borrasca-Fernandes Carla[23]	Temporal evolution of dermo-necrosis in loxoscelism	III-2	C	Cohort	Anti-loxosceles serum
Malaque Ceila M. S[24]	Impact of antivenom administration on the evolution of cutaneous lesion loxoscelism	III-2	C	Cohort	Anti-loxosceles serum
Isbister Geoffrey K.[25]	Funnel-web spider bite. A systematic review of recorded clinical cases	III-3	C	Systematic review	Anti-loxosceles serum
Manriquez Juan J.[26]	Cutaneous and cutaneous-visceral loxoscelism: a systematic review	III-3	C	Systematic review	Combination therapy‡
Hobbs Gregory D.[27]	Comparison of hyperbaric oxygen and dapsone therapy for Loxosceles envenomation	II	B	Randomized clinical trial	Hyperbaric oxygen vs. dapsone
Phillips Scott[28]	Therapy of brown spider envenomation. A controlled trial of hyperbaric oxygen, dapsone, and cyproheptadine.	II	B	Randomized clinical trial	Hyperbaric oxygen vs. dapsone vs. cyproheptadine
Maynor M. L.[29]	Brown recluse spider bites. Beneficial effects of hyperbaric oxygen	II	B	Randomized clinical trial	Hyperbaric oxygen
Hadanny Amir[30]	Non-healing wounds caused by brown spider bites: application of hyperbaric oxygen therapy	III-1	C	Non-randomized clinical trial	Hyperbaric oxygen
Del Puerto Constanta[31]	Experience in cutaneous and visceral cutaneous loxocellularism	IV	D	Case series	Combination therapy‡

Continue Table 5: Summary of the studies included for the qualitative review with methodology used and methodological quality.

Main author	Title	Level of evidence	Grade of recommendation	Type of study	Intervention
Mold James W[32]	Management of brown recluse spider bites in primary care	IV	D	Case series	Combination therapy‡
Schenone H[33]	Loxoscelism in Chile: epidemiological, clinical and experimental studies	IV	D	Case series	Combination therapy‡
Wong S. Lindsey[34]	Loxoscelism and negative pressure wound therapy (vacuum-assisted closure): A clinical case series.	IV	D	Case series	Negative pressure (vacuum-assisted closure)
Chrysostomou D[35]	Spider bite wounds can silver help	IV	D	Case series	Nanocrystalline silver

* Surgical treatment: decompressive fasciotomies, necrosectomies, and posterior coverage (flaps and grafts). ‡ Combined therapy: dapsone, chlorphenamine, systemic corticosteroids, antibiotics, antihistamines.

bite with closure in a second surgical time by suture or graft, another by late incision three to 10 weeks after the bite and closure in a single surgical time, and the last in late incision three to 11 weeks after the bite with graft placement in two surgical times. He presented 33 patients with *L. reclusa* spider bites. Of these, 11 cases were hospitalized and received conservative treatment; seven were managed by early exeresis, and the other 15 had late incisions. The authors concluded that early excision of lesions larger than 1 cm was the best treatment once an area of necrosis greater than 1 cm (0.39 inches) has developed and should be performed within the first week after the bite or whenever gangrene appears to be inevitable so that infection, disability, pain, drainage, and expense are minimized. The area of necrosis and underlying tissue (fat and fascia) should be excised early; secondary closure is usually best performed three to five days later using a partial-thickness graft—an identical wound healed in a few weeks.

Rees[18] conducted a non-randomized clinical trial comparing 31 patients divided into two groups: 14 were treated with early surgical excision of the necrotic papule followed by primary (n = 1) or delayed closure without (n = 3) or with skin grafting (n = 10); the other 17 were treated with the leukocyte inhibitor, dapsone, followed by late surgical excision. Late wound healing (n = 5) and objectionable healing (n = 7) occurred as complications in the first group. In the second group, pretreatment with dapsone decreased the incidence of wound complications (n = 1) and objectionable scarring (n = 1) ($p < 0.05$) while reducing the need for surgical excision (n = 1).

Staneff and collaborators,[19] in a series of cases, described the use of surgical treatments based on decompressive fasciotomies, necrosectomies, and subsequent coverings with flaps and grafts in seven cases of patients with cutaneous loxoscelism accompanied by necrotizing fasciitis of the affected limb for the management of these complications. The authors recommended a clinical-surgical treatment protocol based on the prevention of compartment syndromes, hemodynamic monitoring and restitution, and measures that favor the regeneration of necrotic tissues since the protocol used had been effective and allowed the clinical recovery of the patients after an average of 11 days of hospitalization.

Medical treatment

Maguiña[20] conducted randomized clinical trials of 39 patients with cutaneous loxoscelism and divided them into two groups, time of illness > 24 hours, but < 5 days. One group of 20 patients received dapsone: 100 mg orally, one daily dose for five days. Another group of 19 patients received chlorphenamine maleate at a dose of 4 mg orally every eight hours. A favorable evolution was considered when the skin lesion at the end of the treatment did not present ulceration or necrosis, and an unfavorable evolution was defined when there was ulceration or skin necrosis to a variable degree. Treatment with dapsone allowed favorable evolution in 18 out of 20 patients, and treatment with chlorphenamine allowed favorable evolution in 10 out of 19 patients; 7.6% (3/39) received anti-loxosceles serum in the first six hours after the event, and 33% (12/39) had received other treatments between one and three doses. They concluded that the use of dapsone was statistically significant in the control of the skin lesion and with better clinical efficacy when compared to chlorphenamine at the dose mentioned. Subsequently, they reported using clindamycin 300 mg orally every eight hours to treat infected ulcers or cellulitis without ulcers for seven days.[21]

Likewise, Rees[22] conducted a clinical trial in 16 patients randomized into three treatment groups: dapsone 250 mg orally once daily (n = 6), brown recluse spider antivenom 2 mg/ml intralesionally (n = 5), or combination therapy (n = 5). All patients were treated with erythromycin. In the results, all groups appear to have achieved equal efficacy; all lesions healed in 20 ± 2 days, except two patients who had significantly more extensive areas of skin necrosis at presentation. Dapsone treatment is less effective once necrosis has occurred; antivenom is more effective in patients who have not yet presented with the clinical lesion and less effective once the inflammatory reaction has developed. The combination of dapsone and antivenom seems to be the most effective therapy since they act through different mechanisms.

A retrospective cohort[23] reported a case series of eight patients with loxosceles with post-bite intervals between 15 and 216 hours. Seven patients were treated with anti-loxosceles serum (AV; median post-bite time = 46 hours). Topical treatment with papain (10 and 3%), an oily essential fatty acid lotion, and mechanical debridement were applied. Two patients were treated with oral prednisone for five days. Complete healing of the lesion ranged from 34 to 98 days after the bite in six patients (median 68 days).

Another prospective observational study[24] concluded that the probability of developing necrosis was significantly lower among patients admitted earlier and those who received anti-loxosceles serum ($p = 0.0245$) with a relatively low rate of adverse reactions. It included 146 patients with a mean time from the bite to the serum administration of 41.6 ± 27.4 hours; a polyvalent arachnid antivenom was administered in 74 (50.7%) cases and not in the other 72 (49.3%). Adjuvant treatment was used in 130 patients (90.9%) with corticosteroids, antihistamines, and analgesics. Among the 74 patients who received anti-loxosceles serum, early and late adverse reactions occurred in seven (9.5%) and four (5.4%).

A systematic review by Geoffrey K. Isbister[25] of a clinical case series evaluated the use of anti-loxosceles serum in 75 patients, including 22 children (range 1-17 years), with a complete response in 97% of the cases identified by experts. Three adverse reactions were recorded in adults: two early allergic reactions (one mild and one with severe systemic effects requiring adrenaline) and one case of serum sickness.

A systematic review[26] of clinical studies compared hyperbaric oxygen therapy, ice, anti-loxosceles serum, dapsone, antihistamines, antimicrobials, dextran, corticosteroids, heparin, nitroglycerin, surgery, acetylsalicylic acid, and exchange transfusion. Through three clinical trials, the author reported that dapsone was associated with fewer local complications than surgical treatment, that it was superior to chlorphenamine for skin lesions, and that there was no difference compared to the use of oral dapsone.

Hobbs[27] conducted a controlled clinical trial to compare the effectiveness of treatment with hyperbaric oxygen (HBO), dapsone and combined management of hyperbaric oxygen with dapsone in 32 piglets that received 15 μl of venom intradermally, divided into four groups: group 1 received no treatment; group 2 received HBO at 2 atm for two hours on days 1-3; group 3 received 50 mg dapsone orally on days 1-3; and group 4 received dapsone 50 mg orally and HBO at 2 atm for two hours on days 1-3. Necrosis and induration were measured on days 1-7, 14 and 21. A difference in induration reduction was observed between group 3 and the control group up to days 7 and 14; the magnitude of the effect was clinically insignificant, whereas treatment with dapsone or HBO or a combination offered little clinical benefit in *Loxosceles* envenomation.

A controlled clinical trial[28] in New Zealand White rabbits divided into four groups was conducted to determine whether hyperbaric oxygen (HBO) at 2.5 atmospheres absolute (ATA) for 65 minutes every 12 hours for two days, dapsone 1.1 mg/kg every 12 hours for four days, or cyproheptadine 0.125 mg/kg every 12 hours for four days decreased the severity of skin lesions resulting from experimental *Loxosceles* poisoning. The groups did not differ significantly concerning lesion size, ulcer size, or histopathologic classification.

A randomized clinical trial[29] on hyperbaric oxygen (HBO) therapy with 41 New Zealand White rabbits that received intradermal injections of venom extract was divided into five groups: 1) no HBO (n = 15); 2) immediate HBO treatment at 2.5 ATA (O_2 100%) (n = 6); 3) immediate HBO with ten treatments at 2.5 ATA (O_2 100%) (n = 9); 4) HBO at 48 hours with ten sessions at 2.5 ATA (O_2 100%) (n = 8); and 5) immediate HBO with regular PO inspired by ten treatments (O_2 8.4%) (n = 3). The results and conclusions were that standard HBO significantly reduced wound diameter at ten days ($p < 0.0001$; ANOVA), whereas hyperbaric treatment with normoxic gas had no effect. Thus, HBO therapy within 48 hours reduces skin necrosis and results in a significantly minor wound.

Hadanny Amir et al.[30] presented an analysis with hyperbaric oxygen therapy (HBOT) with two absolute atmospheres of 100% oxygen per day for 13, 17, and 31 sessions in three healing brown spider bite patients two to three months after the failure of other treatments. All wounds were hypoxic ($TcPO_2$ G40 mmHg in room air) with marked improvement during HBOT ($TcPO_2$ 9,200 mmHg). In all three patients, it culminated in complete resolution with satisfactory healing, and no further surgical procedures were required. No patient had significant side effects. The authors conclude that HBOT benefits non-healing wounds when ischemia is the rate-limiting factor in tissue regeneration; with little evidence of other effective treatments, HBOT should be considered a valuable therapeutic tool for these ulcers.

There were three case series on combination therapy (antibiotic, dapsone, systemic corticosteroids, topical nitroglycerin, and high-dose vitamin C). The first case series[31] included 17 patients hospitalized with a diagnosis of loxoscelism, where 82.3% (n = 14) corresponded to cutaneous loxoscelism; an average of 2.5 days elapsed between the bite and hospitalization with a range between one and five days. All cases were managed with intravenous antibiotic therapy; 94% were treated with systemic corticosteroids (hydrocortisone or prednisone 0.5 to 1 mg/kg/day) for seven days; 64.7% with dapsone 50-150 mg per day for four to six weeks. Fifty percent of patients with cutaneous loxoscelism who received concurrent corticosteroids and dapsone had complete healing of the lesion at one month of treatment. Four patients received systemic steroid therapy without dapsone, and 75% of them presented a complete resolution at one month of evolution. The authors recommend combined therapy with supportive measures, antimicrobials, systemic corticosteroids, and antihistamines. The second case series, published by James W Mold,[32] analyzed four treatments (corticosteroids, dapsone, topical

nitroglycerin, and high dose vitamin C) in 262 patients where systemic corticosteroids and dapsone were associated with slower healing. Predictors of healing were increased severity, necrosis, and diabetes. Dapsone was associated with a higher likelihood of healing. The mean time to healing was 22.1 ± 18 days, and the median and range of healing times were 17 days and 1 to 144 days, respectively. With practice, patient management was not significantly better ($p < 0.1061$). The third case series[33] involved 216 loxosceles patients under management with injectable antihistamines or corticosteroids and anti-loxosceles serum in two cases. The local and general manifestations attenuated within 12 hours after the start of treatment, so they recommend early initiation of treatment.

S. Lindsey Wong[34] published an eight-case series on negative pressure treatment using vacuum-assisted closure (VAC) in patients who developed an area of necrosis surrounded by erythema with progression to an open wound. All wounds stabilized and showed progressive healing after the institution of VAC. None of the wounds worsened or failed to respond once VAC treatment was initiated.

Chrysostomou D[35] presented 11 cases of suspected spider bites, to which he applied nanocrystalline silver (Acticoat™) to the affected area. Eight lesions showed favorable evolution, healing without scarring in one week; the remaining three evolved to a sphacelated wound that required additional wound treatment. The author recommended using nanocrystalline silver in arachnoid-inflicted wounds, as it has proven beneficial in achieving symptom control with shorter healing time and reduced or eradicated inflammation and pain.

DISCUSSION

Cutaneous loxoscelism continues to be a clinical entity with a wide margin of variation in therapeutic decisions made in healthcare centers and even in official literature such as seen in clinical practice guidelines. The present discussion aims to compare the scientific evidence published so far, regardless of the frequency with which specific interventions are indicated in clinical practice.

Surgical management

Surgical treatment has been specifically addressed in two studies selected in our review. The first by Auer et al. compared early incision with late incision combined with closure or grafting; in both scenarios, most cases were cured; however, they reported a lower incidence of complications in the early incision scenario compared with late incision. These results support the performance of early surgical treatment within the first ten days of the onset of the clinical event; however, the study is not broadly descriptive in addressing the effectiveness of the intervention and neither the adverse effects derived from either intervention, which limits the strength of the reported data. A second study by Rees and associates compared the performance of an early surgical strategy versus an initial scheme of medical treatment followed by a delayed surgical approach. In the first scenario, they found a higher incidence of prolonged periods of wound healing exceeding six weeks and an argumentative healing process; in the second scenario, they found shorter healing times with better healing results. Both studies showed contradictory results; however, the cases included had specific essential differences. The first study used an early surgical approach to the incision within the first ten days, while the second one used it within the first 48 hours; the late surgical approach in the first study was considered from three to 10 weeks after the initial event, while in the second one, it was from 14 days onwards. The evidence offered by both studies seemed to show that there is a period in which the surgical approach is beneficial in patients, and this occurs after the first 48 hours and before ten weeks, a comprehensive period that requires lines of research focused on the establishment of a more precise period to establish a firm indication about when surgical therapy surpasses medical therapy in treating cutaneous variants of loxoscelism.

Medical treatment

Medical therapeutics in the included findings also appears to have a time-effectiveness relationship. The studies reviewed demonstrated positive effects with dapsone, especially in cases where it is indicated before completion of maturation process of the lesion, showing less remarkable effects once a necrotic eschar has been established. Critical adverse effects reported with dapsone include its hemolytic effects with secondary lowering of hemoglobin levels,[36] and somatic effects such as headache, asthenia, and abdominal discomfort.[36,37] In patients with clinical stability and without hemolytic comorbidities, and with cutaneous variants of loxoscelism, it is the initial therapy that showed the most positive evidence. Its combination with other therapies had different results; in one of the studies, the combination of dapsone with antihistamines, steroids, and hyperbaric oxygen showed no difference in terms of lesion progression compared to cases treated with dapsone only; differently, the use of dapsone together with anti-loxosceles serum therapy showed better results compared to cases treated only with dapsone in another study by Rees and collaborators.[18] The other interventions were reported to be useful in other ways, such as chlorphenamine controlling pruritus. The use of steroids in the results presented may be associated with long healing times; however, it is difficult to establish a clear relationship due to the low level of evidence shown in the studies used.

Overall, the therapeutics of loxoscelism have little strong quality evidence to establish safe recommendations for interventions. Surgical therapy may be harmful if performed too early but may be beneficial within a window of time that has not yet been specified. Medical therapy seems to have more evidence for using dapsone and anti-loxosceles serum to prevent the progression of skin lesions. In contrast, more studies are still needed to demonstrate better the benefit or risk of other therapeutic measures, such as antihistamines and steroids, as well as other therapies that have been used in the later period with a focus on improving the healing of established wounds, such as hyperbaric oxygen or electrical therapy.

The review presented here shows certain limitations. First, the process was carried out ordinarily by the reviewers without using computer systems to facilitate the classification of the bibliography; therefore, the selection of the articles for this review is influenced by the human factor in the selection of the studies. In some cases, the selection was limited by language; most of the bibliography was included in Romance and English; however, the interpretation of texts in other languages was limited. We extend this line of research to the realization of clinical trials that compare the effectiveness of early surgical management. The establishment of medical therapies reported to date or, in its absence, the elaboration of descriptive clinical guides, for example, the current Mexican Clinical Practice Guide for Diagnosis and Treatment of Venomous Spider Bites[38] has been updated more than ten years, something very similar is seen at an international level, especially in the treatment section, without transparent management in cases of cutaneous loxoscelism.

CONCLUSIONS

Cutaneous loxoscelism is a pathology that requires effective and timely management. However, most published studies correspond to a low level of evidence and degree of recommendation, and few studies have been performed to date that allow the development of a therapeutic strategy; due to the methodological characteristics, the study is limited to making recommendations based on contrasted evidence against other therapeutic strategies, since there are few documented clinical trials performed so far.

Whether there is concrete evidence comparing the effectiveness of surgical management over medical treatment depends on the time of evolution, the presence of necrosis, and the size of the ulcer. The available evidence on surgical management guidelines is reported in cases of necrotic ulcers or gangrene measuring equal to or larger than 1 cm. Ideally, early surgical

excision, decompressive fasciotomies, and necrosectomies are recommended in the first surgical stage in these cases to prevent the appearance of compartment syndromes and later evaluate, depending on the area of necrosis, the application of flaps and grafts.

In terms of evolution, the effectiveness of surgical management offers better results in not less than 48 hours due to the complications presented. However, it shows better results within the first week or in less than ten days when dapsone can be applied to reduce the appearance of surgical wound complications or the need for surgical excision.

Among the available information, the combination of initial simultaneous management between dapsone and anti-loxosceles serum with or without application of hyperbaric oxygen at 2.5 atmospheres with 100% O_2 seems beneficial since no significant differences in the size of the ulcer are documented in an early period; even so, HBO is beneficial in this sense two to three months later or, in open wounds, the application of a negative pressure system. Chlorphenamine was documented to be less effective in the treatment of skin lesions. Nanocrystalline silver can be used simultaneously with other measures, as well as supportive measures, antimicrobials, systemic corticosteroids, and antihistamines to manage symptoms to decrease healing time, inflammation, and pain.

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Funding: the study has not received any financial contribution.
Disclosure: the authors declare no conflicts of interest.

Correspondence:
Aldo Israel Olán-De Los Santos
E-mail: aldoi27@hotmail.com