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REVIEW ARTICLE

Thalidomide in the Treatment of Endometriosis Pain:
A Scoping Review of Experimental Studies

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Highlights:
1. Thalidomide has antiangiogenic and anti-inflammatory effects, improving pain.
2. There is a shortage of studies on thalidomide's role in pain management.
3. Thalidomide may become an option in the treatment of endometriosis pain.

ABSTRACT

This study aimed to investigate the applicability of thalidomide in the treatment of pain induced by endometriosis in animals. A scoping review was conducted following the Joanna Briggs Institute method and adhering to Prisma – ScR standards. Searches were performed in six electronic databases using specific descriptors and keywords, employing a Boolean search strategy aimed at retrieving studies on endometriosis, pain, pain management, and thalidomide. The study included data from studies conducted in Iran (n = 1, 50%) and Turkey (n = 1, 50%). All articles (n = 2; 100%) were published in English within the past decade. In studies comparing thalidomide to placebo, a significant reduction in inflammatory factors was observed, which correlated directly with improved clinical outcomes in pain management. This reduction provided additional benefits, including reduced levels of growth factors and regulation of the metalloproteinase (MPP) cycle. The review of studies revealed the anti-angiogenic and anti-inflammatory properties of thalidomide, suggesting its potential as a viable option for pain management. However, the existing literature on thalidomide for this purpose remains limited.

Keywords: pain; pain management; endometriosis; thalidomide.

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INTRODUCTION

Endometriosis is one of the most common gynecological diseases in the world and its pathogenesis is not yet fully understood. It is known that there is an abnormal activity of the immune system, which causes an overactivation of inflammatory factors, culminating in the onset of the disease, which quickly leads to acute and intense pain crises in the pelvic and abdominal region[1,2].

Metalloproteinases are the main enzymes associated with the pathogenesis of nociception in endometriosis, as they initiate the local inflammatory process. It is responsible for the destruction of the epithelial structure of the endometrium, facilitating the adhesion and invasion of ectopic cells into the peritoneal lining, a cyclical process that, if left untreated, leads to the clinical worsening of pain in the disease[3].

The relationship between pain and endometriosis is more evident in the chronic phase of the disease, where it acquires neuropathic characteristics, with changes between nerve fibers in the injured regions, along with the density and quality of synaptic transmission[4]. It is also observed that there is an increase in angiogenic activity in the region of the lesion, which intensifies the inflammatory effect due to the greater disposition of factors coming from the circulation. The sum of the two effects, stimulated in the long term, develops the chronic form of endometriosis, which makes treatment difficult[5].

The main challenge in the treatment of endometriosis in its chronic form is the episodes of refractory pain observed in this stage of the disease. Hormone blockers are commonly used as a therapeutic alternative, but their spectrum of action does not include an analgesic effect on this type of pain, hence the need to look for other options[6,7].

Thalidomide is a synthetic derivative of glutamic acid with an unknown mechanism of action. It is thought to reduce the levels of several cytokines such as tumor necrosis factor (TNF), in addition to inhibiting interleukin 12, which affects the reduction of lymphocyte proliferation. This has a good effect on the treatment of pain with nociceptive characteristics and, in the long term, reduce the factors responsible for the chronification of pain in endometriosis. The use of this drug is common in the field of oncology due to its antiangiogenic effect, which significantly reduces the percentage of tumor growth. In the case of endometriosis, this effect can be beneficial by reducing the flow of inflammatory factors and cells responsible for maintaining tissue inflammation[1,8].

METHOD

Protocol

This scoping review was conducted and presented according to the Joanna Briggs Institute Methodology, in addition to the Prisma – ScR standards. It has been also registered in OSF Home, with access link: osf.io/s23e6. All descriptors were validated by searching Health Sciences Descriptors, Medical Subject Headings and Embase Subject Headings before searching the databases[9-12].

Inclusion criteria

During the review, the PCC framework was applied: P representing population/patients, C representing concept, and C representing context. This methodology guided the formulation of the research question, data collection, and inclusion criteria for studies. By aligning the focus of this study with the PCC strategy, the primary question emerged: “What experimental evidence exists regarding thalidomide’s efficacy in treating endometriosis-associated pain?” The defined parameters were as follows: animals with induced endometriosis constituted the population, pain crises linked with inflammatory conditions represented the concept, and the utilization of thalidomide for pain management served as the contextual framework (Figure 1).

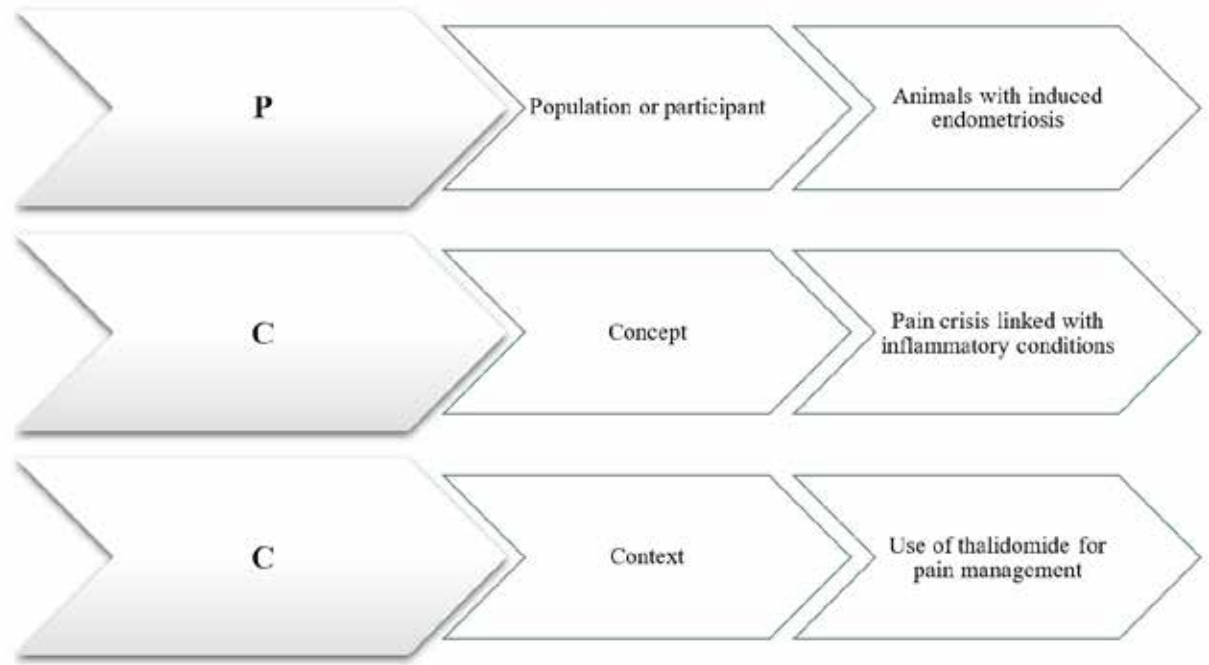

Figure 1 – Flowchart for guiding question selection and initial database search adapted from Prisma[11].

Only studies involving animals afflicted by endometriosis-induced pain crises, with pain management as their primary focus, were selected. Accepted study designs included experimental and quasi-experimental approaches, encompassing randomized clinical trials, non-randomized trials, before-and-after studies, and interrupted time series studies. Additionally, selected studies had to demonstrate pain control as an outcome through treatment with thalidomide.

Data sources

The chosen databases included Medline via PubMed, Scopus, Excerpta Medica Database (Embase), Latin America and the Caribbean Literature on Health Sciences (Lilacs), Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full Text, Google Scholar, and grey literature sources.

Search strategy

Searches were conducted across six electronic databases using a combination of descriptors and keywords, employing a Boolean search strategy designed to target specific conceptual domains related to endometriosis, pain, pain management, and thalidomide. Articles in any language were included, with no restrictions on publication dates, to ensure comprehensive coverage of relevant studies. The search was conducted between February and December 2022, applying a filter to retrieve articles with available abstracts for subsequent analysis, as outlined in Table 1.

Table 1 – Records identified through search strategies in electronic databases

BASIS	SEARCH STRATEGY	RECORDS FOUND
PubMed	endometriosis AND thalidomide	4
Embase	endometriosis thalidomide	28
LILACS	endometriosis thalidomide	1
Scopus	endometriosis thalidomide	28
Cochrane	endometriosis thalidomide	0
Web of Science	endometriosis thalidomide	11
Subtotal		72
	NEW TERMS ACCORDING TO SYNONYMS – MeSH/DeCS/EMTREE	
PubMed	(Sedoval OR thalomide OR thalidomide) AND (Endometrioses OR Endometrioma OR Endometriomas OR endometriosis)	4
Embase	(Sedoval OR thalomide OR thalidomide) AND (Endometrioses OR Endometrioma OR Endometriomas OR endometriosis)	115
	Usado os filtros = animal experiment OU animal model	4
LILACS	(Sedoval OR thalomide OR thalidomide) AND (Endometrioses OR Endometrioma OR Endometriomas OR endometriosis)	1
Scopus	(Sedoval OR thalomide OR thalidomide) AND (Endometrioses OR Endometrioma OR Endometriomas OR endometriosis)	28
	Usado os filtros = animal OR animals OR in vitro study OR disease models, animal OR animal model	12
Cochrane	(Sedoval OR thalomide OR thalidomide) AND (Endometrioses OR Endometrioma OR Endometriomas OR endometriosis)	0
Web of Science	(Sedoval OR thalomide OR thalidomide) AND (Endometrioses OR Endometrioma OR Endometriomas OR endometriosis)	11
	Animal OR in vitro	5
	TOTAL FINDINGS with MeSH/DeCS/EMTREE filters and synonyms	180

Selection of evidence sources

Two types of searches were conducted: one using general terms to broaden the scope and identify potential literature for comparison with the inclusion criteria, yielding 72 articles. A second search using more specific terms yielded an additional 180 articles, all of which were included in the general search results. The 180 records were imported into the Mendeley desktop reference manager, where 95 duplicates were removed, resulting in 85 summaries available for analysis. Following a review of titles and abstracts, 59 records were excluded, leaving 26 articles for full-text analysis.

These 26 studies were evaluated against the eligibility criteria by three independent examiners, resulting in the inclusion of 16 articles. Subsequently, 14 articles were excluded, resulting in a total of 2 articles eligible for the study (Table 1). This selection process is outlined in a flowchart (Figure 2), created according to the Prisma guidelines[11].

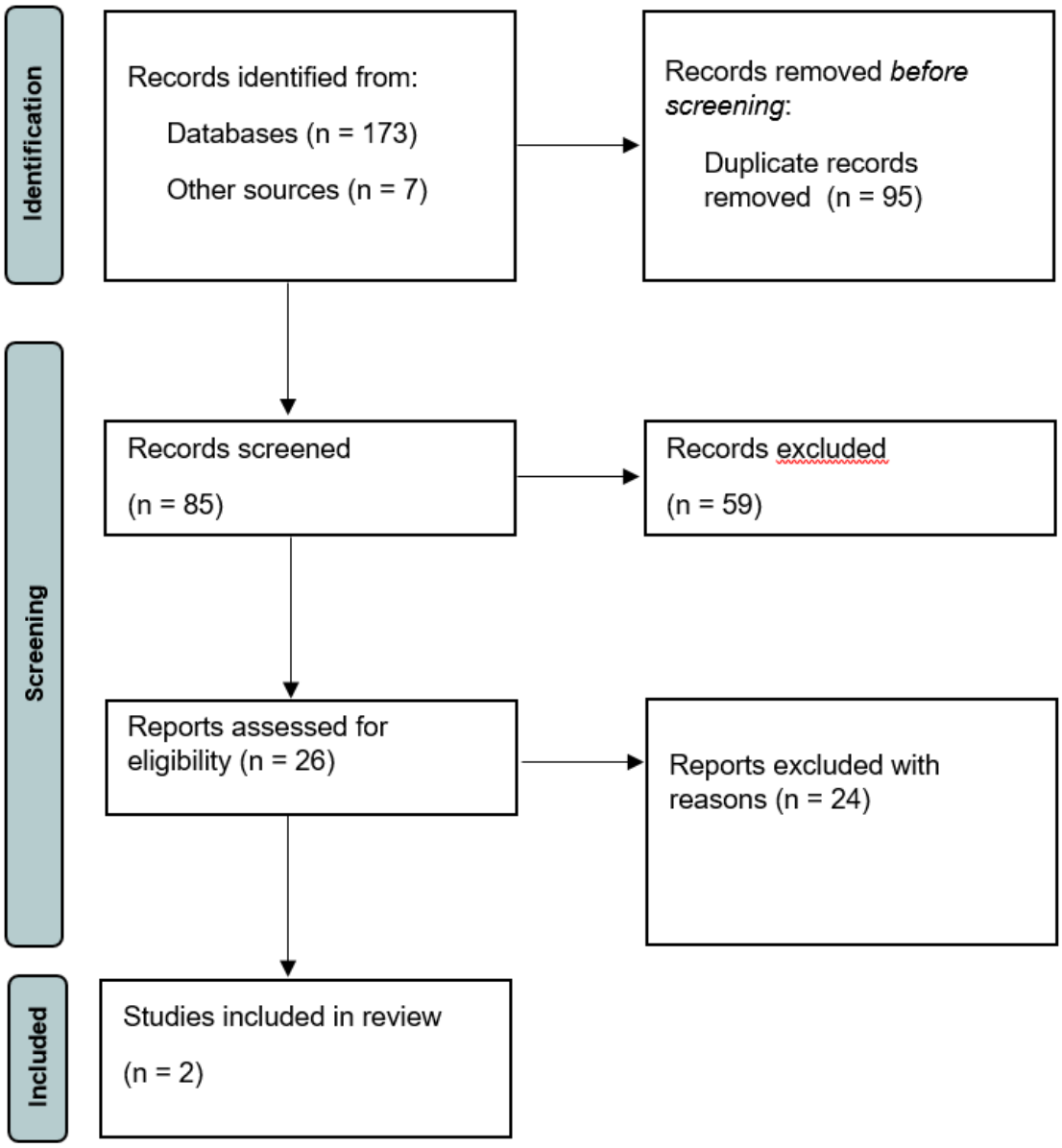

Figure 2 – Flowchart of study selection process.

Extraction procedure

Data extraction was conducted subsequent to a comprehensive review of the full articles, with prior consideration of the application of inclusion and exclusion criteria. This process was carried out by three independent reviewers, each assigned to two databases. A database was structured in table format using Microsoft Excel 2010 software, with information arranged in the following sequence: author/year, objective, medication, sample size (n) and study type, population studied, study context, evaluation of thalidomide use, pros and cons of thalidomide use, =results, and study selection status.

Summary of results

The data were analyzed and presented in the text using descriptive statistics, presenting absolute and relative frequencies. SPSS Statistics 25.0, 2017 software was used for the analyses.

Results

The two trials included in this review showed 100% success in the use of thalidomide as a therapy for pain control. The studies are randomized experimental trials, and their detailed summary is shown in Chart 1.

Author/ year	Objective	Medicine	n	Study design
Azimirad et al.1	Evaluation of the effect of thalidomide in rats with endometriosis induced after surgery	Thalidomide	23	Randomized clinical trial
Bakacak et al.13	Evaluation of the effect of thalidomide in rats with endometriosis induced after surgery	Thalidomide	8	Randomized clinical trial

Chart 1 – Articles included in the study.

The study countries were: Iran (n = 1, 50%) and Turkey (n = 1, 50%). All articles (n = 2; 100%) were published in English. Regarding the year of publication, they were all published in the last 10 years.

In studies where there is a comparison between thalidomide and placebo, it is observed that there is a high response associated with the reduction of inflammatory factors, directly affecting the clinical improvement of pain conditions with benefits that lead to the reduction of growth factors and control of the metalloproteinase cycle (MPP). Confirming that the results have statistically significant mean differences, Bakacak et al.[13], when inducing endometriosis in rats and treating them with thalidomide 100 mg/kg (n=8) and control (n=8) with saline solution 0.5 ml/kg by oral gavage, observed that there was a significant decrease in the average implant volume in the group administered with thalidomide after treatment (53.3 and 22.9 mm 3, respectively, p=0.0[12]). The differences observed in the histopathologic scores of the thalidomide group (3 vs. 1, p=0.012) were not observed in the control group. Decreases in VEGF-A and myeloperoxidase (MPO) levels were observed (p=0.004 and p=0.037, respectively).

In support of the study by Bakacak et al.[13], Azimirad et al.1 also proves the analgesic, anti-inflammatory and antiangiogenic efficacy of thalidomide by showing in an experimental clinical trial that the use of the drug at a dose of 22 mg/day resulted in a decrease in VEGF, IL-6 and the number of leukocytes and specific lymphocytes (p=0.07; 0.07; 0.02; 0.01 and 0.001), respectively, in the peritoneal fluid of rats with induced endometriosis compared to a control group.

DISCUSSION

Efficacy of thalidomide in the management endometriosis pain

Pain in endometriosis is the result of the action of metalloproteinases that initiate the pain cascade from the inflammatory cycle, with multiple changes occurring in the peritoneal cavity. There is an activation of several chemokines and cytokines involved in the stimulation of local nociceptors responsible for the painful condition of endometriosis[3,5].

Among the cytokines responsible for nociceptive activation, we can mention prostaglandins, histamine and bradykinin, which are inflammatory mediators that cause vasodilation and allow capillary permeabilization, facilitating the entry of cells of the leukocyte system from peripheral tissues to initiate and maintain the nociceptive condition. The cells of the leukocyte system are responsible for maintaining the inflammatory state by providing cytokines such as TNF-alpha, IFN-gamma, interleukins, VEGF (vascular endothelial growth factor), which are important for maintaining the inflammatory state[6,7].

Among the studies reviewed, there is a consensus on the anti-inflammatory action or effect on inflammatory and growth factors that contribute to the clinical improvement of pain, illustrating the efficacy of thalidomide in endometriosis pain crises[1,13].

The implantation of ectopic cells in the endometrial cavity leads to an inflammatory process through the production of pro-inflammatory cytokines and prostaglandins and the suppression of anti-inflammatory interleukins. Azimirad et al.[1] demonstrated the efficacy of the anti-inflammatory and antiangiogenic activity of thalidomide by showing in an experimental clinical trial that the use of the drug at a dose of 22 mg/day resulted in a decrease in VEGF (vascular endothelial growth factor), IL-6, and the number of leukocytes in the peritoneal fluid of rats with induced endometriosis compared with a control group. In this study, contrary to the literature, the effect on TNF-alpha could not be demonstrated and the authors considered this result to be a methodological error.

Bakacak et al.[13] in a similar study demonstrated that there was a decrease in the volume of implants in the group treated with thalidomide at a dose of 100mg/kg/day for 4 weeks in relation to the control, as well as a reduction in VEGF and oxidative markers, suggesting that it is effective in the inflammatory phenomenon of endometriosis, confirming previous research.

CONCLUSION

The results of this scoping review show a paucity of experimental studies on the use of thalidomide for the treatment of pain in endometriosis, which is a limitation of this review. However, the anti-angiogenic and anti-inflammatory effects of the drug have been demonstrated, which could be an option for use as a pain treatment.

However, there is little information on long-term use and a lack of standardization of doses, which makes it difficult to establish a protocol for using this drug in experimental models. Therefore, it is suggested that more research of this type be conducted in order to improve and supplement the scientific evidence and allow the therapeutic use of thalidomide for pain relief.

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Maria do Socorro de Sousa Cartágenes: project administration, supervision, writing – review & editing.

João Batista Santos Garcia: project administration, supervision, validation, writing – review & editing.

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