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REVIEW

Clinical results of infrared coagulation as a treatment of high-grade anal dysplasia: a systematic review

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Abstract

Background Anal intraepithelial neoplasia (AIN) (or low/high grade squamous intraepithelial neoplasia (L/HSIL)) is the precursor of anal of early invasive anal cancer. Different treatment options for local ablation of localized lesions have been reported. The aim of this study was to analyze the clinical efficacy and safety of infrared coagulation for the treatment of anal dysplasia.

Methods A search of the literature was performed in 2019 using PubMed and Cochrane to identify all eligible trials published reporting data on the treatment of anal dysplasia with infrared coagulation. The percentage of squamous cell carcinoma of the the anus that developed in the follow-up and results on major complications after treatment were the primary outcomes.

Results Twenty-four articles were identified from which 6 were selected with a total of 360 patients included, with a median age of 41.8 years. Three studies were prospective and 3 retrospective, only one was a randomized trial. All articles included males, 4 articles included HIV-positive women and only one article included non HIV infected males. No patient developed major complications after infrared coagulation therapy. Pain was the most common symptom found after the procedure in the different series and mild bleeding that did not require transfusion was the most common complication occurring in 4 to 78% of patients. Median follow-up was between 4.7 and 69 months. No patient developed squamous cell carcinoma after infrared treatment. Recurrent HSIL varied from 10 to 38%. Two studies reported results from follow-up of untreated patients showing that between 72 and 93% of them had persistent HSIL at last follow-up and 4.8% developed squamous cell carcinoma.

Conclusions Infrared coagulation is a safe and effective method for ablation of high-grade anal dysplasia that could help prevent anal cancer. Continued surveillance is recommended due to the risk of recurrence.

Keywords Anal dysplasia · Infrared coagulation · High resolution anoscopy · Anal intraepithelial neoplasia

Introduction

Anal intraepithelial neoplasia (AIN) is the precursor of early invasive anal cancer which today is preferentially called superficially invasive squamous cell carcinoma of the anus (SISCCA) defined as having ≤ 3 mm stromal invasion and a maximal horizontal spread of ≤ 7 mm [1]. AIN and can be classified according to the Richart grading scale (AIN I/II/III) or the Bethesda system (low-grade squamous intraepithelial lesion and high-grade squamous intraepithelial lesion, LSIL/HSIL). It is well known that human papilloma virus (HPV) is the etiologic agent for this and other several specific squamous cell cancers [2]. Although the natural history of anal cancer is not fully understood, the persistence of HPV infection is a prerequisite for abnormal anogenital cytology [3].

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Men who have sex with men (MSM) and most individuals with human immunodeficiency virus infection (HIV) have a higher prevalence and incidence of anal canal and perianal HSIL [4]. The incidence of SISCCA has been increasing in HIV-infected individuals, even after the introduction of highly active antiretroviral therapy, although the incidence of other virus-associated malignancies has decreased in these patients. In fact, the incidence in HIV-positive MSM is estimated to be 80 times higher than the incidence in men in the general population [3].

Treatment of AIN in its early stages could be the best management to avoid progression to SISCCA [5]. Different treatment options for local ablation of localized lesions have been reported. Laser therapy, cryotherapy, electrocautery, infrared coagulation (IRC), wide excision and topical agents (imiquimod, trichloracetic acid, and 5% 5-fluorouracil cream) [6–11]. However, none of them are standardized.

IRC was first described in the late 1970s and it was first used for AIN during the 1990s. Lesions have to be identified first by high-resolution anoscopy (HRA), and then IRC is applied.

IRC ablation has been established as an effective treatment for HSIL. This treatment can be applied in an outpatient setting with local anesthesia and is associated with a low rate of complications. This is why it is widely used. However, recurrence as potential drawback some years after its introduction into clinical practice, some studies were published showings the clinical efficacy or effectiveness of IRC in the management of these lesions [12–17].

The aim of the present review was to analyze the clinical efficacy and safety of IRC for the treatment of AIN.

Materials and methods

Protocol and registration

The authors developed the protocol for review, in accordance with the 2009 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [18] guidelines also using the new reporting elements derived from the 2016 PRISMA harms checklist [19].

Eligibility criteria

Study characteristics

Study characteristics were defined using the PICOS framework. Search term definitions were inclusive, promoting a sensitive search of studies reporting infrared coagulation for the treatment of AIN.

Population The review aimed to identify studies of patients with AIN.

Intervention IRC as a treatment of AIN.

Comparisons Studies were eligible regardless of whether they were retrospective or prospective in design, controlled or uncontrolled.

Outcomes Studies were eligible if they provided extractable data on the percentage of anal cancer developed during follow-up and results on complications described as minor or major complications according to Clavien–Dindo classification (minor complication: grade I–II; major complication: grade III–V).

Report characteristics

Year of publication Any publication date was eligible as covered by database search from 1960 to 2019.

Language It was decided to include only studies with full text in the English language.

Type of study Only peer-reviewed publications reporting primary data were eligible. Thus reviews, editorials, letters and other forms of secondary expert opinion were excluded at the screening stage. Only full manuscripts were eligible; thus conference abstracts and proceedings were also excluded. No constraint was imposed based on level of evidence. This decision was taken with the knowledge that the vast majority of data would be extracted from case series rather than higher quality study types.

Information sources

The authors performed a comprehensive search of the literature on May 2019 using PubMed and Evidence Based Medicine reviews (including the Cochrane database of systematic reviews and the Cochrane central register of controlled trials). The search terms were “infrared coagulation”, “infrared coagulator”, “anal dysplasia” and “anal intraepithelial neoplasia”.

Study selection

Screening was performed at the abstract level by the authors, excluding studies not meeting eligibility criteria where this could be readily determined from the abstract alone. Full-text copies of all remaining English language studies were obtained and assessed by reviewers. A second search was carried out identifying other references from the selected studies, from the initial search.

Individual study quality and risk of bias

The methodological quality of all individual included studies was assessed by the authors and classified in accord with Oxford Centre for Evidence-based Medicine (CEBM) levels of evidence definitions for 'therapy or harm' [19]. The following rules were applied accepting that distinguishing study designs can be problematic for observational studies [20].

Results

The literature search identified 25 articles in the first search. Nineteen studies were excluded after reading the title and the abstract because they did not fit in the inclusion criteria, shown in Fig. 1. Therefore, 6 articles were selected and a total of 524 patients were included in the review [12–17].

The characteristics of the selected series are provided in Tables 1 and 2. They were published between 2008 and 2018. Three studies were prospective and three retrospective. Only one of them was a randomized open trial. Five

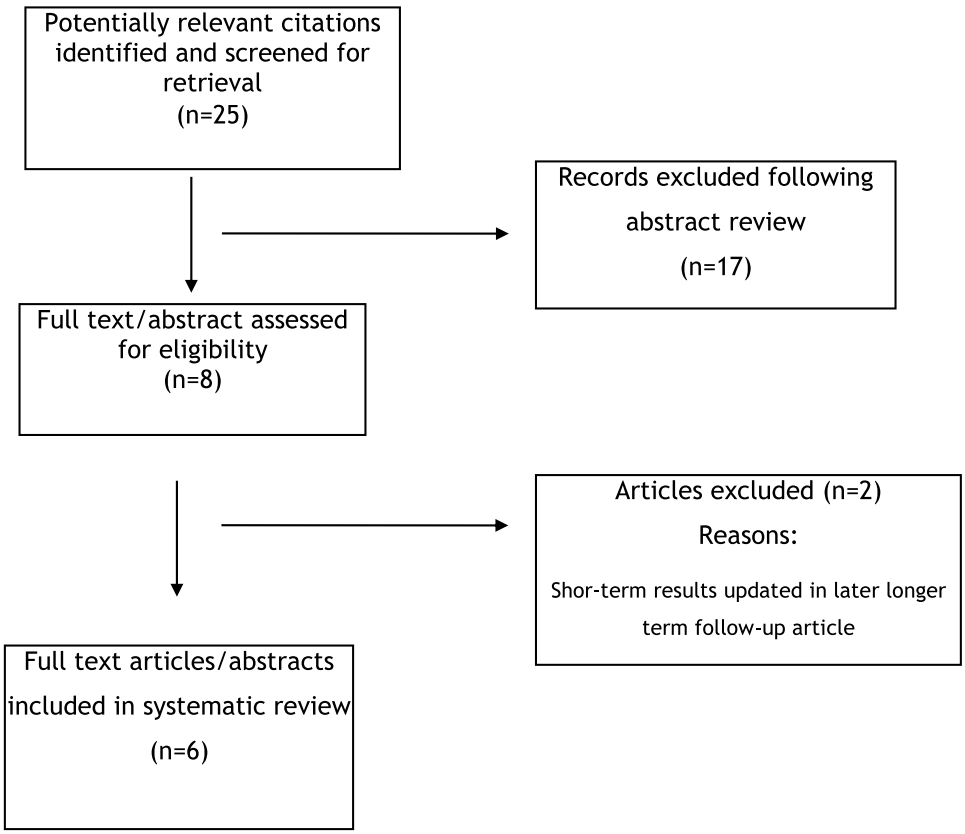

Fig. 1 Flowchart showing study selection process

Table 1 Characteristics of the studies included in the systematic review

Study	Year	Patients included	Data analysis	Study	Level of evidence[a]
Stier et al. [12]	2008	18	Prospective	Clinical series	2C
Cranston et al. [13]	2008	68	Retrospective	Clinical series	2C
Goldstone et al. [14]	2011	96	Retrospective	Clinical series	2C
Weis et al. [15]	2012	146	Prospective	Clinical series	2C
Sirera et al. [16]	2013	56	Retrospective	Clinical series	2C
Goldstone et al. [17]	2018	120	Prospective	Randomized, open-label trial	1B

[a]According to Oxford CEBM classification [18]

Table 2 Characteristics of the patients included in the series

Study	Study population	Baseline histology	Age[a], years (range)
Stier et al. [12]	16 M HIV 2 F HIV	HSIL	44 (32–53)
Cranston et al. [13]	68 MSM HIV	HSIL	45 (28–65)
Goldstone et al. [14]	52 MSM HIV− 44 MSM HIV+	HSIL	36 (23–72)
Weis et al. [15]	99 M HIV 25 F HIV 42 Untreated	HSIL	40 (27–70)
Sirera et al. [16]	45 M HIV 11 F HIV	HSIL (AIN II/III)	42 (22–58)
Goldstone et al. [17]	112 M HIV 8 F HIV	HSIL	49 (25–78)

MSM men who have sex with men, *M* male, *F* female, *HSIL* high-grade squamous intraepithelial lesion, *AIN* anal intraepithelial neoplasia

[a]Median

of these articles were from the United States and one from Spain.

Only four articles included women ($n = 46$), all of them HIV infected. The other two only included men, but one of them differentiated between HIV-infected MSM and HIV-negative MSM.

The population in this review had a median age of 41.8 years. All patients were treated with IRC and none of them had any major complications.

Regarding complications related to the procedure, there were no major complications according to Clavien–Dindo classification that required any intervention (grade III–V). Pain was the most common symptom found after the procedure in the different series and mild bleeding that did not require transfusion was the most common complication. These results are shown in Table 3.

The median follow-up of series included was between 4.7 and 69 months. Clinical response to treatment was assessed by cytology and histology in most of the series. If the biopsy proved a normal result or LSIL, the lesion was considered healed. If the biopsy showed an HSIL from the treated area at the first evaluation, then it was considered persistence of the disease. If treated area showed a complete response at a follow-up visit and then showed an HSIL at a later evaluation, the lesion was classified as recurrent.

Just in one study [14] the cytology result by itself was also considered during the follow-up for classifying as persistence or recurrence of disease. HSIL at last follow-up varied from 12.5 to 38% in patients with HIV infection. In the only study that included patients without HIV, HSIL was ≤ 10%, compared to 18% in HIV positive patients in the same study although the difference was not statistically significant. No patient treated with IRC developed anal cancer during this period of time (as shown in Table 4). Two studies [15, 17] reported results from follow-up of untreated patients showing that between 72 and 93% of them had persistent HSIL at last follow-up and 4.8% developed squamous cell carcinoma.

Discussion

The treatment of HSIL remains controversial. Many options are described in the literature but there is no agreement on which is the best form of management. IRC is a useful and safe method for treating anal canal dysplasia and to prevent its progression to SISCCA [5]. As we found in this review, IRC is a safe treatment with a reported recurrence rate from 10 to 38% in the literature [12–17]. Continued surveillance is necessary following the initial treatment because of the risk of recurrence.

The use of trichloroacetic could be a reasonable option for small lesions. It has been reported to cause regression to normal epithelium or LSIL in 71–79% [21, 22]

Table 3 Complications and adverse events related to infrared coagulation

Study	Mild/moderate anal pain	Mild/moderate bleeding	Mild/moderate fecal incontinence[a]	Anal stricture	Local infection	Other complications (flatulence, anal mucous discharge)
Stier et al. [12]	22%/33%	61%/5%	11%[a]/0	0	0	16%
Cranston et al. [13]	0	0	0	0	0	0
Goldstone et al. [14]	Most common	NE	NE	NE	NE	NE
Weis et al. [15]	NR	NR	NR	NR	NR	NR
Sirera et al. [16]	13%/0	4%/0	0	0	0	0
Goldstone et al. [17]	80% (mild or moderate)	78% (mild or moderate)	NE	NE	NE	NE

NE not specified, *NR* not reported

[a]Short-lived mild fecal incontinence within a few days to several weeks after the procedure

Table 4 Clinical results in the different studies included

Study	HSIL at last follow up	Duration follow-up	Developed SISCCA *N* (0%)
Stier et al. [12]	38%	12 m	0/18 (0%)
Cranston et al. [13]	36%	4.7 m	0/68 (0%)
Goldstone et al. [14]	HIV+ 18%	HIV+ 69 m	0/96 (0%)
	HIV− 10%	HIV− 48 m	
Weis et al. [15]	Treated 13%	Treated 1.3 y	0/102 (0%)
	Untreated 93%	Untreated 1.8 y	2/42 (4.8%)
Sirera et al. [16]	12.50%	25 m	0/56 (0%)
Goldstone et al. [17]	Treated 29%	Treated 2 y	0/51 (0%)
	Untreated 72%	Untreated 1 y	0/57 (0%)

HSIL high-grade squamous intraepithelial lesion, *HIV* human immunodeficiency virus, *m* months, *y* years

Trichloroacetic is applied directly to the lesion in different sessions at 1- to 2-month intervals.

Other ablative techniques such as electrocautery may also be a good choice. A study of 232 MSM (132 HIV positive and 100 HIV negative) had demonstrated 75–85% of healed lesions after the first treatment but with a recurrence rate of 6% and 53% respectively during follow-up [23]. Pineda et al. [5] in 2008 presented a series of 197 treated patients showing 57% recurrence after a median follow-up of 19 months. Forty-six patients (18.7%) required staged therapy for persistent disease. Despite treatment, three patients progressed to anal cancer or SISCCA. Complications were described in nine patients (4%) including bleeding, anal stricture and anal fissure.

Most of the studies are focused on HIV-positive men and little is known in HIV-positive women. Future studies should include series of HIV-positive women to know more about the utility of the screening programs and the treatment of HSIL and its influence on the natural history and progression to anal cancer. Also other populations at risk of anal cancer like those with iatrogenic immunosuppression (e.g., solid organ transplant recipients, inflammatory bowel disease patients on long-term oral corticosteroids) have to be considered.

Few studies published to date report data regarding the quality of life of patients after treatment. Overall reporting of side effects is poor and non-standardized. This has also to be evaluated since it could be something to take into account when deciding which treatment to use.

As far as we know, this is the first systematic review of the literature in this topic, following the PRISMA methodology. However, the present study has some limitations. The studies that were found are very heterogeneous. Some included only HIV-positive men, others both HIV-positive men and women and others included MSM also. Also while some included patients with an isolated lesion, others included patients with diffuse HSIL of the anal canal [24]. Little information is given in the different trials about fecal continence after the treatment.

In this review, the majority of the series reported had a follow-up lasting over a year except for that of Cranston and colleagues [13]. In their series, the average interval between IRC treatment and follow-up biopsy to check efficacy was 140 days (4.7 months) (range 37–831 days). In this case, it is difficult to determine if the 36% of inefficacy of IRC is due to recurrence or persistence of the disease.

We have noticed the lack of articles about the treatment options of HSIL. More prospective and randomized studies should be designed to determine the most appropriate technique for the treatment of this disease. IRC is one useful technique but there are also topical treatments such as trichloroacetic acid, fluorouracil or imiquimod, or other ablative therapies such as cryotherapy, laser and electrocautery fulguration.

Conclusions

Infrared coagulation is an effective method of ablation of HSIL that could help to prevent anal cancer. Due to the risk of recurrence of the disease, continued surveillance is recommended so that metachronous lesions do not progress to SISCCA. Future prospective and randomized trials are needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval As this was a systematic review of existing studies ethical approval was not required.

Informed consent For this type of study formal consent is not required.

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