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REVIEW ARTICLE
Reconstructive

Intralesional Cryotherapy for the Treatment of Keloid Scars: Evaluating Effectiveness

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Background: Intralesional (IL) cryotherapy is a novel treatment technique for keloid scars, in which the scar is frozen from inside. Over the past decade, several studies have been published with varying outcomes. A critical analysis of the current literature is, therefore, warranted to determine whether IL cryotherapy is an alternative to established keloid scar treatments.
Methods: A comprehensive review was performed, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. PubMed and EMBASE were searched from inception. Studies and level of recommendation were graded according to the American Society of Plastic Surgeons criteria.
Results: Eight studies meeting the inclusion criteria were selected. The average scar volume decrease ranged from 51% to 63%, but no complete scar eradication was achieved on average. Scar recurrence ranged from 0% to 24%. Hypopigmentation posttreatment was seen mostly in Fitzpatrick 4–6 skin type patients. Finally, complaints of pain and pruritus decreased significantly in most studies.
Conclusions: IL cryotherapy for the treatment of keloid scars shows favorable results in terms of volume reduction and alleviated complaints of pain and pruritus. However, no complete scar eradication is established, and recurrences are seen. Also, persistent hypopigmentation proved a problem in Fitzpatrick 4–6 skin type patients. Summarized, the evidence proved limited and inconsistent resulting in an American Society of Plastic Surgeons grade C recommendation for this type of treatment of keloid scars. *(Plast Reconstr Surg Glob Open 2015;3:e437 doi: 10.1097/GOX.0000000000000348; Published online 24 June 2015.)*

In predisposed individuals, injury of the skin can lead to an abnormal healing response, resulting in keloid scars.[1] Besides aesthetic disfigurement, keloids can cause major physical complaints of pain and pruritus, hence impairing the quality of life of the patient.[2] The treatment of keloids is a great challenge, as surgical excision alone results in high recurrence rates (>60%) and even growth stimulus following treatment.[1] To date, several treatment modalities exist, but not a single treatment option has proven widely effective.[3,4] First-line nonsurgical treatment options include silicone sheeting, pressure therapy, intralesional (IL) corticosteroids, and IL 5-fluorouracil.[3,5] The evidence for effectiveness of silicone sheeting and pressure therapy remains limited.[5] IL corticosteroids and 5-fluorouracil have proven successful in reducing pain and pruritus, as well as decreasing scar volume. However, several painful treatment sessions are required and recurrence rates remain high.[4]

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If these nonsurgical treatment options fail, surgical excision with adjunctive radiation is considered the most effective treatment protocol.[6] It allows for complete scar eradication with low recurrence rates.[7] This therapy is, however, not suitable for children (<12 years) or patients with keloids that cannot be closed primarily or are located near radiosensitive organs such as the thyroid gland.[8]

CRYOTHERAPY

Recently, a novel technique for the treatment of keloids was introduced offering a potential treatment modality between the current nonsurgical and surgical treatment options: IL cryotherapy.[9] For decades, liquid nitrogen has been applied externally to freeze and destruct keloids. However, numerous side effects, such as hypopigmentation, blistering, delayed healing, and infection, were reported.[10,11] Furthermore, treatment of larger keloids required multiple cryotherapy sessions.[10,11]

To solve these problems, IL cryotherapy was introduced by Weshahy.[9] By using a hollow needle, a cryogen can be applied directly into the deeper dermis of the scar. In this way, all the pathological tissue will be frozen and destructed, creating a new scar without keloidal characteristics, while sparing the surface epithelium.[12] IL cryotherapy thus claims to enhance volume decrease while reducing the risk of hypopigmentation and other surface reactions.[13]

Working Mechanism

The working mechanism by which cryotherapy destructs the keloid scar relies on 2 phases of cellular destruction: a physical phase and a vascular phase.[11,14] During the physical phase, rapid freezing causes direct cell injury through the formation of sharp ice crystals. Moreover, the differential freezing of cell compartments leads to changing osmotic gradients and electrolyte imbalances, causing irreversible cell damage. In the vascular phase, damage to and failure of the microcirculation lead to cell destruction through ischemic necrosis.[11,14]

The working mechanism by which cryotherapy prevents the keloid from recurring can be explained from 2 perspectives. First, histological studies have shown cryotherapy to result in rejuvenation of the scar tissue. Freezing pathological scar tissue induces the differentiation of abnormal keloidal fibroblasts toward a normal phenotype.[15,16] In vitro, cryotherapy has been shown to result in normalizing the synthetic activity of keloid fibroblasts.[16] After treatment, the ratio of type III to type I collagen is increased, resembling normal healthy tissue.[17]

Second, the absence of wound contraction following a freezing injury may be another explanation. In burns, wound contraction results in severe scarring and contractions.[18–20] After freezing of a wound, however, no wound contraction is seen.[18–20] The cellular matrix remains following cryotreatment and acts as a scaffold for cellular regeneration, enhancing wound repair.[18–20] This may prevent recurrence, as high-tension locations are prone to keloids.[21]

Systematic Review

Several studies investigating IL cryotherapy have been published. Remarkably, quite different outcomes were reported by these studies, especially in terms of recurrence rate and of incidence of hypopigmentation. In order to evaluate the effectiveness of IL cryotherapy, an overview of the current literature is required. This article discusses the findings of a systematic review to answer the question: Is IL cryotherapy an alternative to other well established keloid scar treatments? And in which role within the current spectrum of treatment modalities should it be positioned?

METHODS

Search Strategy

A comprehensive systematic review of the English-language literature was performed, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. PubMed and EMBASE were searched from inception to August 2014. The following terms were used as index terms or free-text words: “cicatrix” or “scars” (including synonyms and closely related words such as hypertrophic scar and keloid scar) and “cryotherapy” or “cryosurgery” or “cryoablation” and “intralesional.” References of retrieved articles were scanned for additional studies. Inclusion criteria consisted of the following: (1) any English-language randomized controlled trials, controlled clinical trials, prospective or retrospective cohort studies, or pilot studies reporting treatment with IL cryotherapy for treatment of scars; and (2) studies including solely keloid scars or studies including hypertrophic and keloid scars. Exclusion criteria were as follows: (1) experimental studies and (2) studies assessing only patient satisfaction, without objective outcome measurements. In case of duplicate articles, only one article was included.

The article screening process was performed as follows: 3 investigators (M.C.E.v.L., A.E.J.B., and J.C.F.K.) carried out the initial searches and 2 investigators (M.C.E.v.L. and A.E.J.B.) independently reviewed the studies for eligibility. Investigators were blinded to each other, meeting only to compare

findings after completing the extraction process. Decisions about eligibility were resolved by discussion. Seventy-six potentially relevant studies were identified from the initial searches. Subsequently, 2 authors (M.C.E.v.L. and A.E.J.B.) independently screened the full-text articles for eligibility using a standardized data extraction form with inclusion and exclusion criteria. Disagreement was resolved through discussion. This resulted in the inclusion of 8 articles (Fig. 1).

Data Extraction

One reviewer extracted data, and a second review author verified the accuracy of the extracted data. Discrepancies in opinion about an article were reviewed, and consensus was achieved through discussion. A standardized data form to capture the following information was used: (1) study characteristics; 2) study participants (including origin or Fitzpatrick score); (3) scar characteristics (duration, location, etiology, and previous treatments); (4) study design (prospective/retrospective and follow-up duration); (4) intervention, including type of device used and number of sessions; (5) assessment/measurement method; and (6) study results, of which the recurrence rate was the main outcome. The data were summarized in an evidence table.

Methodological Quality Assessment

Heterogeneity in study design and outcome measures did not allow for quantitative pooling of data for meta-analysis. The level of evidence of the extracted studies was graded according to the American Society of Plastic Surgeons Rating Levels of Evidence.[22] This classification assigns each article to a corresponding level of evidence ranging from I (highest) to V (lowest). We classified a level II to prospective studies, which used a definition for inclusion of keloid scars and clearly defined their outcomes measurements including a definition for scar recurrence. Also, a minimum of a 1-year follow-up was required.[23,24] Finally, a practice recommendation was concluded based on the collected evidence according to the American Society of Plastic Surgeons Grade Recommendation Scale.[22]

RESULTS

Study Characteristics

Initial database searches identified 77 potentially relevant studies. Two studies accepted for publication were also included.[25,26] Thus, 79 articles were screened on the basis of title and 28 articles on the basis of the abstract, and finally, 24 full-text articles were analyzed (Fig. 1). Excluded records did not investigate the effect of IL cryotherapy in patients or studied other treatment modalities such as external cryotherapy. One excluded study reported solely subjective outcomes, and 1 study investigated only the pigmentation change following treatment.[27,28] Finally, 8 articles met all inclusion criteria. A summary of the included studies is given in Table 1.

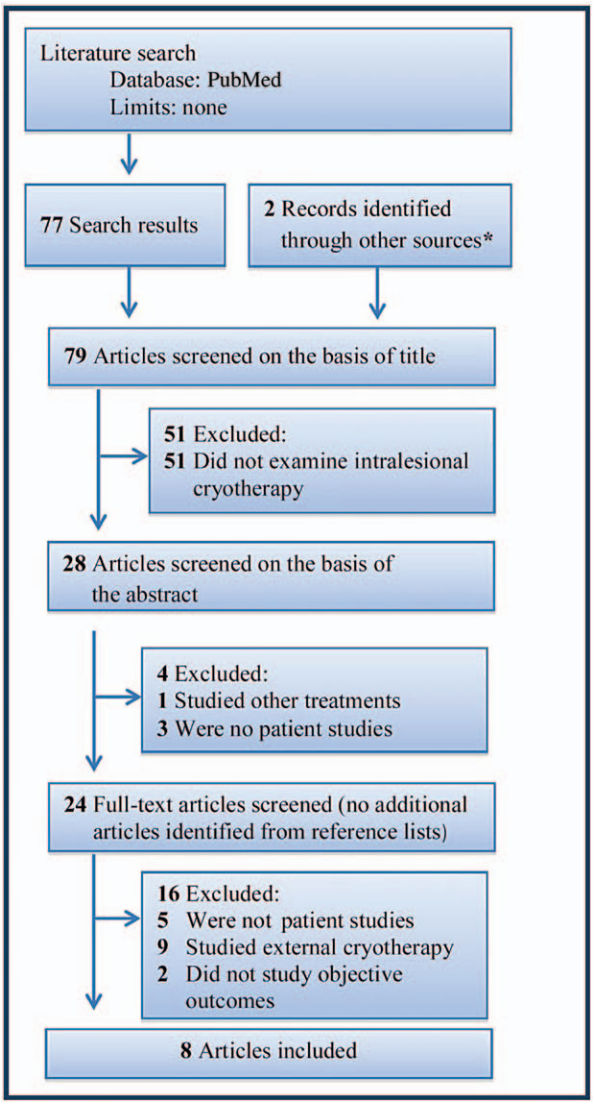

Fig. 1. Flow diagram of the search and selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis. *2 accepted records, included from the VU Medical Center Research database.[25,26]

Methodological Quality

Most studies were prospective of nature, but they did not differentiate between keloid and hypertrophic scars ($n = 2$), lacked a definition for scar recurrence ($n = 6$), or did not respect the minimum of a 1-year follow-up posttreatment ($n = 3$). Therefore,

Table 1. Summary of the included studies.

Study	Study Type	N (P/S)	Scar Type	Skin Type*	Follow-up (Range)	Cryodevice	Protocol	Outcome Measures	Assessment	Results	Level of Evidence†
Gupta and Kumar[12,32]	Prospective	12/12	Keloid scar	NS	7–12 mo	Nitrogen based, multiple lumbar puncture, and/or hypodermic needles	Monthly ILC session: >5, <10	Volume reduction	NS	7/12 patients: >–75% 4/12 patients: –51% to 75% 1/12 patients: –40%	III
								Pain + pruritus	NS	12/12 patients: disappeared	
								Hypopigmentation	NS	12/12 patients: persistent	
								Recurrence	NS	0%	
Har-Shai et al[13]	Prospective	10/12	Keloid + Hypertrophic scars	F1–3	18 mo	Nitrogen based, double-lumen cryoneedle	1 treatment session	Volume reduction	Putty water displacement method	–51% ($P < 0.002$)	III
								Pain	Rating: 0–3	–78% ($P = 0.005$)	
								Pruritus	Rating: 0–3	–62% ($P = 0.005$)	
								Hardness	Rating: 0–3	–72% ($P = 0.002$)	
								Redness	Rating: 0–3	–52% ($P = 0.01$)	
								Recurrence	NS	0%	
								Hypopigmentation	NS	No permanent depigmentation	
Zouboulis et al[30]	Pilot study	10/10	Keloid scar	F1–6	6 mo	Nitrogen based, 20-gauge metallic cryoneedle	Monthly session: >3, <6	Volume reduction	NS	2/10 patients: –50% to 100% 5/10 patients: <–50% 1/10 patients: 0% 2/10 patients: increase	IV
								Hypopigmentation	NS	40%	
								Recurrence	NS	0%	
Stromps et al[29]	Retrospective	21/32		F1–6	18.62 mo (12–24)	Nitrogen based, double-lumen cryoneedle + silicone sheeting	1–2 sessions: 2nd at 6 mo if no sign volume reduction	Volume reduction	Putty water displacement	Earlobe + face: –89%	III
								Hardness	mGGS	Improvement, $P < 0.0012$	
								Pain	mGGS	Improvement, $P < 0.0233$	
								Discomfort	mGGS	Improvement, $P < 0.02$	
								Recurrence	NS	0%	
								Hypopigmentation	NS	3/21 patients: temporary	
Har-Shai et al[17]	Prospective	9/10	Keloid scar	F1–3	15 mo	Nitrogen based, double-lumen cryoneedle	1 treatment session	Volume reduction	Putty water displacement	–67.4% ($P < 0.005$)	III
								Pain	Rating: 0–3	–78% ($P < 0.004$)	
								Pruritus	Rating: 0–3	–52% ($P < 0.016$)	
								Hardness	Rating: 0–3	–72% ($P < 0.004$)	
								Redness	Rating: 0–3	–83% ($P < 0.007$)	
								Recurrence	NS	0%	
								Hypopigmentation	NS	No marked hypopigmentation	

(*Continued*)

Table 1. (*Continued*)

Study	Study Type	N (P/S)	Scar Type	Skin Type*	Follow-up (Range)	Cryodevice	Protocol	Outcome Measures	Assessment	Results	Level of Evidence†
Weshahy and Abdel Hay[31]	Prospective	22/25	Keloid + Hypertrophic scars	F2–4	7–36 mo	Nitrogen based, Weshahy cryoneedles + triamcinolone injections	1 ILC + < 8 ILCS	Volume reduction	Alginoplast + saline	−94% ($P < 0.001$)	III
								Pain	Rating: 0–3	−100% ($P < 0.001$)	
								Pruritus	Rating: 0–3	−100% ($P < 0.001$)	
								Hardness	Rating: 0–3	+92% ($P < 0.001$)	
								Redness	Rating: 0–3	−81% ($P < 0.001$)	
								Recurrence	NS	12%	
								Hypopigmentation	NS	21/35 patients: temporary 7/35 patients: persistent	
Van Leeuwen et al[26]	Prospective	27/29	Keloid scar	F1–6	12 mo	Liquid nitrogen, double-lumen cryoneedle	1–2 sessions: 2nd at 6 mo, if <50% volume decrease	Volume reduction	Putty plaster displacement	−63%; *r*, 16–100 ($P < 0.01$)	II
								Redness	Dermaspectrometer	Returned to pretreatment value, after initial increase	
								Elasticity	Cutometer	+57%	
								Pain	POSAS	−45%	
								Pruritus	POSAS	−28%	
								Overall improvement	POSAS	Doctor: +24% Patient: +52%	
								Recurrence	‡	24%	
								Hypopigmentation	>1% surface	9/29 patients: persistent	
								Complications		7.5% wound infection	
Van Leeuwen et al[25]	Prospective	25/30	Keloid scar	F1–6	12 mo	Argon gas to induce freezing and helium for thawing; 17-gauge cryoneedle	1 session	Volume reduction	Putty plaster displacement	−62.1%	II
								Redness	Derma spectrometer	No change	
								Elasticity	Cutometer	+36%	
								Pain	POSAS	−35%	
								Pruritus		−33%	
								Overall scar appearance	POSAS	Doctors: + 9% Patients: +32%	
								Recurrence	‡	17%	
								Hypopigmentation	>50% surface	11/30 patients: persistent	
								Complications		10% wound dehiscence	

N (P/S) indicates number (N) of patients and scars (S) (Patients/Scars); ILC, intralesional cryotherapy; ILCS, intralesional corticosteroid injection; mGGS, modified Gorney Gram scale; NS, not specified in study.

*Fitzpatrick skin type ranging from 1 to 6.

†According to American Society of Plastic Surgeons Rating Levels of Evidence and Grading recommendations for Diagnostic studies, V is lowest level of evidence and I is highest.

‡Judgment of recurrence, defined as a growing, pruritic, and nodular scar as described by Cosman and Wolff.[24]

only 2 studies were classified as level of evidence type II, 5 as type III, and 1 as type IV (Table 1).

Patient Characteristics

The sample size of the included studies ranged from 9 to 27 patients (mean, 17±7.4). In total, 136 patients with 160 lesions were treated. Follow-up ranged from 6 to 21.5 months with a mean follow-up of 14.5±5.3 months. Patient's origin or Fitzpatrick skin type was described in 7 of 8 studies; van Leeuwen et al,[25,26] Stromps et al,[29] and Zouboulis et al[30] included a mixed population including all races. Har-Shai et al[13] included mostly white patients. When looking at the Fitzpatrick skin type score, 2 studies included a Fitzpatrick (F) 1–3 skin type patient population,[13,17] 1 study a F2–4 population,[31] and 4 studies included a F1–6 population.[25,26,29,30]

Treatment Modalities

The included studies used different treatment devices. Most studies used nitrogen-based cryodevices: Gupta and Kumar[12] used simple lumbar puncture or hypodermic needles. Zouboulis et al[30] used a flexible metallic cryoprobe stem and Weshahy and Abdel Hay[31] designed "Weshahy cryoneedles." Har-Shai et al[13] used a disposable 14-gauge double-lumen cryoneedle called the CryoShape (Etgar Group International Ltd, Kfar Saba, Israel). van Leeuwen et al[25,26] used the same device but also tested an argon gas–based cryoneedle called IseSeed (Galil Medical, Yokneam, Israel). Most studies evaluated treatment outcomes after a single cryosession, but some used up to 10 sessions. Finally, Weshahy and Abdel Hay[31] and Stromps et al[29] combined IL cryotherapy with adjuvant therapy with silicone sheeting and triamcinolone injections, respectively.

Recurrence and Volume Decrease

Scar recurrence following treatment ranged from 0 up to 24%, with a mean of 7.6% ± 10.1%. Weshahy and Abdel Hay[31] reported small recurring scars (0.5–1 cm^3) at the periphery in 12% of the scars, which disappeared gradually through repeated IL steroid injections. Zouboulis et al[30] reported a volume increase following treatment in 2 patients (20%) but did not reported any recurrences. One study did not report the incidence of scar recurrence.[32]

Volume decrease was measured differently by the included studies: van Leeuwen et al.[25,26] made a mold of the scar using dental putty. Thereafter, the mold was filled with plaster and weighed to obtain the volume. Har-Shai et al,[13] Stromps et al,[29] and Weshahy and Abdel Hay[31] filled the mold with saline to measure scar volume. Har-Shai et al[13] and van Leeuwen et al[26] reported a mean volume decrease ranging from 51.4% to 63% (range, 16–100). Stromps et al[29] reported a 89% volume decrease for facial scars, while presternal scars showed only 47% volume decrease. See also Table 1.

Elasticity

A 36% and 57% elasticity increase was showed in 2 studies, in which an objective measurement devices were used.[25,26] Other studies measured improvements ranging from 71% to 92%, using nonspecified elasticity or hardness measurement methods.

Pigmentation and Redness

Har-Shai et al[13,17] reported no permanent or marked hypopigmentation in white patients following treatment in both studies. In contrast, van Leeuwen et al[25,26] reported hypopigmentation in most scars following treatment in a patient population including patients of all Fitzpatrick skin types. Although hypopigmentation recovered in the majority of scars, persistent hypopigmentation was seen after 12 months in both studies (31%[26] and 37%,[25] respectively). Other studies did not clearly describe whether the hypopigmentation persisted and to what degree.

Two studies measured an increase in redness following treatment. After 12 months, however, redness returned to pretreatment values.[25,26] Other studies reported redness to decrease with 52–83% following treatment.

Scar Assessment

Subjective scar evaluation improved in all studies, although 3 studies did not quantify their results. Complaints of pain decreased with a mean of 52.5% ± 18.4% (range, 35–78) after treatment, and itching decreased with 43.6% ± 15.8 % (range, 28–61), but never disappeared completely. Two studies showed an improvement according to patients and doctors using the Patient and Observer Scar Assessment Scale (POSAS). Patients and doctors scored an improvement of 32% and 9% following treatment with the argon gas–based device and a 52% and 24% improvement with the liquid nitrogen-based device, respectively.[25,26]

Fitzpatrick Skin Types

Most studies treated white (F1–3) patients. Two studies included a F1–6 patient skin type population and reported some remarkable differences in outcomes among patients with diverse skin types.[25,26] First, persistent hypopigmentation was mainly seen in F4–6 skin type patients. Compared with F1–2 patients, there was a significantly higher incidence of hypopigmentation in F5–6 patients ($P = 0.02$).[25,26]

Second, F1–2 scars showed a statistically significant greater improvement in subjective scar evaluation compared with F5–6 scars, as measured with

the POSAS by doctors (P = 0.03) and patients (P = 0.04).[25,26] In addition, high odds ratios were seen for recurrence in F3–4 (56%) and F5–6 (66%) patients, compared with F1–2 patients.[25,26]

Complications

All studies reported mild-to-moderate postoperative pain with local edema and superficial necrosis in the first weeks following treatment. Wound infection and wound dehiscence were reported by 2 different studies, in 7.5% and 10% of the patients, respectively. Both were successfully treated conservatively.[25,26]

DISCUSSION

IL cryotherapy is designed to destroy the core of the keloid, while at the surface, cells including melanocytes are much less affected.[17] As such, IL cryotherapy aims to enhance volume reduction and decrease recurrences while minimizing the risk of hypopigmentation. Although studies were initially promising, recent studies provided different insights. This article addresses the question whether this treatment is an alternative to other keloid scar treatments.

Treatment Protocol

Although most studies were prospective, only 2 were classified as level II evidence studies. Other studies were graded with a lower classification due to various limitations: First, most studies did not meet the minimum criterion of a 1-year follow-up.[33] This is essential to reliably assess scar recurrences. Second, many studies did not use a definition to distinguish keloid and hypertrophic scars. This is relevant, as hypertrophic scars have a better prognosis than keloid scars.

Finally, to quantify outcome measurements, validated and reliable subjective and objective scar measurement tools should be used. Examples are the Cutometer for scar elasticity,[34] the Dermaspectrometer for scar color,[35] and the POSAS for subjective scar assessment by doctor and patient.[36,37]

The use of definitions and measurement devices will enhance reliable assessment of treatment outcomes and can make comparison of study results possible.

Devices

A number of devices have been described for the treatment of keloid scars with IL cryotherapy. However, only 2 devices are currently commercially available: a liquid nitrogen-based device[13] and an argon gas–based device.[25] The liquid nitrogen-based device is a double-lumen 14-gauge cryoneedle. The cryoneedle is connected via an elongation tube to a simple Dewar cylinder, in which liquid nitrogen is stored. After pressure has built up inside the cylinder, the liquid nitrogen is forced through the cryoneedle, which freezes along the entire track.

Van Leeuwen et al[25] reported freezing capacity problems with the above-described liquid nitrogen system. When treating large or multiple keloid scars, elongated or even dysfunctional treatments were observed. Therefore, they tested another and novel system based on argon gas.[25] With this system, high-pressurized argon gas (300 bar) is led through a 17-gauge disposable cryoneedle. This results in a rapid freezing process only at the tip of the needle (as opposed to the nitrogen-based cryoneedle which freezes along the total track of the needle). In addition, the freezing process is monitored and can be adjusted to control the procedure. Also, a thawing cycle can be induced via the same needle using helium gas, to allow for the gentle removal of the cryoneedle from the frozen tissue. It should, however, be mentioned that the costs of the argon gas–based system exceed the liquid nitrogen-based device significantly.

Volume and Recurrences

Most studies reported >50% volume decrease following treatment. However, on average, there was no complete scar eradication in the included studies. Even after a maximum of 10 sessions of IL cryotherapy in the study by Gupta and Kumar,[32] no complete eradication was achieved. It is therefore questionable whether IL cryotherapy will achieve the same results as excision of the scar, even after multiple sessions. More likely, IL cryotherapy will result in an "acceptable" volume reduction as with nonsurgical treatments like corticosteroid injections.

Although some studies did not report any recurrences, others reported a recurrence ratio up to 24%. Two factors can account for this inconsistency: First, some studies did not respect the minimum of a 1-year follow-up, as discussed above. Second, most studies reporting low or no recurrence ratios included only white patients. In contrast, 2 studies reported increased odds ratios for recurrence in F3–4 and F5–6 patients, compared with F1–2 patients.[25,26] The relation between recurrence and a Fitzpatrick score of more than 3 is described by other authors as well.[38] Therefore, it is important to include a patient population consisting of all Fitzpatrick skin types.

Persistent Hypopigmentation

IL cryotherapy was designed to overcome pigmentation disorders associated with external cryotherapy. Many authors, therefore, encouraged the use of IL cryotherapy for dark-skinned individuals suffering from keloid scars.[27,28] In a controlled study, van Leeuwen et al[26] demonstrated a significantly higher incidence in F5–6 patients compared with

F1–2 patients in a patient population consisting of all Fitzpatrick skin types. Other studies also confirmed the incidence of persistent hypopigmentation following IL cryotherapy. However, it was not always reported clearly whether the hypopigmentation remained and to what degree. In our clinical center, we experienced that any hypopigmentation is considered as very disturbing or even traumatic for patients. As clinical studies reported hypopigmentation in patients with a Fitzpatrick of more than 3, we advise to use IL cryotherapy in those patients only when the scar is nonvisible (eg, retroauricular).

CONCLUSION

This systematic review showed IL cryotherapy to be a promising treatment modality for the treatment of keloid scars in terms of volume reduction and alleviation of pain and pruritus. However, on average, no complete scar eradication is attained and scar recurrence is seen. Also, persistent hypopigmentation remains problematic in nonwhite patients. These issues raise the question whether IL cryotherapy is a viable treatment alternative to other established scar treatments.

To make IL cryotherapy a worthwhile treatment, novel systems or adjustments of the existing systems are required to obtain complete scar eradication, lower the recurrence rates, and control hypopigmentation. Also, high-quality randomized studies will have to generate stronger evidence proving the effectiveness of IL cryotherapy and its safety in the different Fitzpatrick skin type groups. The evidence provided by the studies included in this review proved limited and inconsistent in terms of effectiveness, resulting in a grade C practice recommendation for IL cryotherapy to date. High-quality randomized studies are required to generate stronger evidence, proving the effectiveness of this technique.

Ultimately, IL cryotherapy could be an addition to the existing keloid scar treatments: (1) if nonsurgical techniques have failed; (2) as combination therapy with nonsurgical therapies as steroid injections[31] or silicone gel sheeting[29]; (3) as alternative for excision with adjuvant irradiation in case radiotherapy is not available or the patient (<12 years) or keloid (size and anatomical location) is not suitable for radiation therapy; and (4) in a specific subgroup of patients seeking alleviation of pain and pruritus rather than complete scar eradication.

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