Adding steroids to lidocaine in a therapeutic injection regimen for patients with abdominal pain due to Anterior Cutaneous Nerve Entrapment Syndrome (ACNES) : a single blinded randomized clinical trial

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ABSTRACT

Background: Anterior cutaneous nerve entrapment syndrome (ACNES) may result in chronic abdominal pain. Therapeutic options include local injection therapy. Data on the efficacy of adding corticosteroids to these injections are lacking.

Methods: Patients >= 18 years with ACNES were randomized to receive an injection of lidocaine with (LC-group) or without (LA-group) the addition of methylprednisolone into the point of maximal abdominal wall pain. Pain was recorded using a Numeric Rating Scale (NRS: 0-10) and a Verbal Rating Scale (VRS: 0 = no pain, 5 = unbearable pain) at baseline and 6 weeks after the start of a bi-weekly injection regimen consisting of a total of 3 injections. A minimal 50% reduction on NRS and/or 2 points on VRS were considered successful responses.

Results: Between February 2014 and August 2016, 136 patients (median age 46 yr, range 18-79, 75% females) were randomized (68 vs. 68). The proportion of patients demonstrating a successful response after 6 weeks did not significantly differ between groups (LA 38%, LC 31%, p=0.61). At 12 weeks, the number of patients still experiencing a minimal 50% pain relief had decreased but no group difference was observed (LA 20%, LC 18%, p=0.80). Minor side effects included temporary increase of pain, tenderness at injection sites or transient malaise (LA23/68, LC 29/68, p = 0.46).

Conclusion: Adding corticosteroids to a lidocaine does not increase the proportion of ACNES patients with a successful response to injection therapy. Lidocaine alone can provide long term pain relief after one or multiple injections, in approximately 1 of 5 patients.

Trial Registration: Nederlands (Dutch) Trial Register, www.trialregister.nl NTR4141

INTRODUCTION

Abdominal wall pain due to anterior cutaneous nerve entrapment syndrome (ACNES) is a potentially debilitating condition that is increasingly recognized in first and second line practices. Patients characteristically complain of one small area of abdominal wall tenderness with typical properties of neuropathic pain such as somatosensory skin disturbances and burning or 'electric' sensations.[1,2] Various treatment options were suggested including injection therapy using local anesthetic agents. Some patients experience a therapeutic effect of one or several peripheral nerve blocks using 5-10 ml of lidocaine. [3,4] More invasive treatment options are pulsed radio frequency treatment (pRF) or a neurectomy of the anterior cutaneous nerve endings. [5,6]

The ideal therapeutic approach for ACNES is minimally invasive. The addition of corticosteroids to a local anesthetic injection may seem logical if one assumes that ACNES is based upon an entrapment mechanism associated with neurogenic inflammation and ischemia.[7] A previous systematic review investigating the effect of corticosteroids addition compared to lidocaine alone in compression neuropathies showed increased pain reduction in the steroids groups although the analyzed studies were of low quality.[8]

The exact mechanism of action of corticosteroids is largely unknown. In general, perineurally administered corticosteroids were found to prolong short term peripheral nerve block analgesia duration with several hours. Moreover, widespread anecdotal evidence suggests that these blocks can exert an effect that largely exceeds the intrinsic half time of corticosteroids and may occasionally result in complete long term pain remission.[9-13] However, the administration of lidocaine alone can also initiate anti-phlogistic effects leading to long term pain relief.[14, 15] One systematic review found that steroids added to local anesthetics did not confer additional benefits in spinal pain syndromes.[16] In our center it is standard practice to treat an ACNES patient with up to three consecutive infiltrations into the point of maximum pain prior to initiate further invasive treatments such as pRF or a neurectomy.[6] The first infiltration using lidocaine is also used as a diagnostic tool to support the diagnosis. Once confirmed, it is usual care to administer consecutive injections using a mix of lidocaine and corticosteroids.

Currently however, the ideal injection regimen for ACNES is unknown. The present single blind randomized clinical trial was aimed to evaluate the efficacy of corticosteroids addition in ACNES patients receiving lidocaine peripheral nerve blocks for this specific abdominal wall pain syndrome.

MATERIAL AND METHODS

This single blind randomized clinical trial was conducted at two Dutch centers: Máxima Medical Center (SolviMáx, Center of Excellence for Chronic Abdominal Wall and Groin Pain), Veldhoven, and Pantein Hospital, Boxmeer. Both hospitals have specialized surgery departments with considerable experience in the treatment of chronic abdominal wall and groin pain syndromes. The Medical Ethics Committee of MMC approved study design, protocol and informed consent procedures. The study was registered in the Dutch Clinical Trial Register (NTR 4141). Design and reporting of this trial were performed according to the CONSORT guidelines.[17]

Study criteria

Patients were eligible for the present study if they were adult (>18 years) and if they reported ≥ 2 of the following signs associated with ACNES:

1. Unilateral, constant site of abdominal tenderness with a small (< 2 cm^2, 'fingertip') area of maximal intensity situated within the lateral boundaries of the rectus abdominis muscle,
2. Tenderness increases by abdominal muscle tensing, while simultaneously pressure is put on the point of maximum pain (Carnett's test),
3. Presence of somatosensory skin disturbances such as altered cool sensation, hypoesthesia or hyperesthesia covering the point of maximal pain and significant abnormal pain while squeezing the abdominal wall skin (pinch test).

Eligible patients were included if a minimal 50% pain reduction within 15 minutes following local infiltration of the point of maximum pain with 5-10 ml of 2% lidocaine (depending on the body weight) was gained. Exclusion criteria were bilateral complaints, pregnancy, recent intra-abdominal pathology, allergy for one of the used substances, previous treatment for ACNES such as pRF therapy or epidural injections, active viral or worm infections, stomach ulcers or recent vaccinations, relevant comorbidity, abnormal blood tests suggestive of some visceral pathology or impaired communication. Study information was provided in the outpatient department and patients were given sufficient time to consider participation. Informed consent was obtained once individuals complied with all study requirements.

Primary and secondary outcome measures

The primary outcome was the proportion of patients achieving a minimal 50% drop in pain score using NRS and/or a minimal 2 points drop using VRS after six weeks of follow-up. Secondary outcomes were the proportion of patients who after 12 weeks still experienced a minimal 50% NRS pain drop and the number of adverse effects. Charac-

teristics including age, sex, body mass index and pain related specifics such as presumed etiology and baseline NRS scores were tabulated for both groups.

Randomization, blinding and treatment allocation

Randomization was performed using computer generated blocks of eight. Stratification occurred for duration of symptoms (<3 months vs. >3 months), participating center (Eindhoven vs. Boxmeer) and whether the primary diagnostic injection had been performed in one of the participating centers or elsewhere (for example by a general practioner), in a 1:1 allocation ratio. Treatment allocation was performed and registered by an independent research assistant. Injections were covered with black tape so the patient could not identify a potential color difference in the mixture. Unblinding was performed after the primary endpoint was reached, while outcomes were assessed by the investigator (FM) and then communicated with the patient.

Follow up

Patients received the allocated treatment in the outpatient department after 2, 4 and 6 weeks. If satisfactory pain relief was obtained by then, an additional follow-up visit at 12 weeks was proposed. Pain intensity was scored at these time points using both a numeric pain rating scale [NRS, 0 (pain absent) to 10 (excruciating pain)] and a verbal rating scale (VRS 0-5, 0 = no pain, 5 = unbearable pain). When patients reported an unsatisfactory result after 6 weeks, they were offered alternative treatment options including pRF or a surgical neurectomy some 6 weeks later.

Specifics of injections

Infiltration of the point of maximal pain can be considered as a modified anterior rectus sheath block. A free hand technique was used in absence of convincing evidence that ultrasound guidance is required for this relative simple needle placement just beneath the anterior rectus sheath, as previously published.[6] The point of maximal pain was confirmed using Carnett's test and marked with a pencil. A subfascial injection of either 5-10 ml of 2% lidocaine (Group LA) or 5-9 ml of 2% lidocaine combined with 40 mg of a methylprednisolone suspension (Group LC) was administered at the marked point of maximal pain with the patient in supine position. The primary investigator (FM) performed the majority of the injections and outcome assessments. Patients were encouraged to resume daily activities as soon as possible.

Statistical analysis

A power analysis based on the authors previous experience revealed that, assuming a 10% success rate in the LA group and a 30% success rate in the LC group, a 2 x 62 sample size was needed (two-sided Fisher's exact test, α err prob = 0.05, Power (1-β err prob)

= 0.80, allocation ratio N2/N1= 1). Including a 10% dropout rate, a total of 136 patients were included in the period between April 2014 and July 2016. Descriptive statistics were used to determine the frequencies of the demographic and outcome variables and to describe measures of central tendency and variability, dependent on the shape of their distribution. The Shapiro Wilk test was used to analyse whether or not parameters were normally distributed.

Differences in proportions between the experimental groups after six weeks were tested using the Fisher's Exact Test. Differences in continuous variables were evaluated using the Independent-Samples Mann-Whitney U test if the parameter was not normally distributed and the Independent-Samples T test if the parameter was normally distributed.

Post hoc binary logistic regression analysis determined whether the allocated group (LA or LC) or other patient characteristics contributed to the prediction of injection therapy success. To prevent overfitting of the model, only parameters with a $p \leq 0.2$ significance level were entered into the final multivariate stepwise binary logistic regression analysis (method Backward Wald) with a probability out of p=0.1. To prevent multicollinearity, pairwise correlations between the parameters to be entered into the final model were calculated. Of pairs with a bivariate correlation of ≥ 0.7, only the parameters with the highest univariate significance levels were entered into the final model. The corresponding odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. An OR > 1.0 indicates a higher chance on therapy success, whereas an OR < 1.0 indicates a lower chance.

Analyses were performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, US).

Role of the funding sources

No funding was used or had any role in study design, data collection, data analysis, interpretation or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Group baseline characteristics were similar as presented in Table 1. Patient flow is presented in figure 1. Fifty and fifty-one of two initial allocated groups of sixty-eight patients reached the primary endpoint according to protocol. Reasons for drop-out were similar in both groups as the majority of these patients did not require a second therapeutic injection because one therapeutic or even only a diagnostic injection provided long lasting pain relief. The distribution of these early responders is presented in figure 2.

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Table 1. Baseline characteristics in ACNES patients receiving injection therapy using lidocaine with (LA) or without (LC) steroids

LA (n=68)	LC (n=68)		
Age[*]		46 (18-79)	43 (18-78)
Sex ratio	F:M	2,8:1	3,5:1
Height (cm)[**]		170 (8)	172 (9)
Weight (kg)[**]		78 (17)	76(17)
BMI (kg/m²)[**]		27 (5)	26 (5)
Etiology (n, %)			
Spontaneous		46 (68%)	44 (65%)
Recent abdominal surgery		16 (24%)	13 (20%)
Pregnancy		1 (1%)	2 (2%)
Unusual activity/sport		2 (2%)	3 (4%)
After a flu		3 (4%)	3 (4%)
Other		0	3 (4%)
Duration of pain prior to enrollment (months)[*]		14 (1- >120)	15 (1- >120)
Presence of local somatosensory disturbances around trigger point (n, %)		44 (65%)	44 (65%)
NRS [*]		7 (4-10)	8 (6-10)
Verbal Rating Scale (n, %)			
0 = No pain		0	0
1 = Very mild		3 (4%)	1 (1%)
2 = Mild		8 (12%)	4 (5%)
3 = Moderate		29 (43%)	23 (34%)
4 = Severe		25 (37%)	33 (49%)
5 = Excruciating		3 (4%)	7 (10%)
Abdominal wall pain location (n)			
Right upper quadrant		13 (19%)	13 (19%)
Right lower		28 (41%)	31 (46%)
Left upper		6 (9%)	3 (4%)
Left lower		21 (31%)	21 (31%)

Baseline patient demographics, pain characteristics and disability scores in ACNES patients receiving two different therapeutic injection regimens.

Abbreviations: LA = lidocaine alone, LC = lidocaine + corticosteroids; NRS = Pain level, Numeric Rating Scale (0, absent-10 unbearable); BMI = Body Mass Index. Data are presented (*) as medians with ranges or IQR (Q3-Q1), (**) means with standard deviations or numbers of cases with percentages, as appropriate.

Both an intention to treat (ITT) and per protocol (PP) analysis were performed. Concerning the primary outcome, the proportion of patients demonstrating a successful response was similar in the LA and LC group (43 and 34%, respectively; p=0.29). Therapeutic success using PP analysis was slightly lower but again no significant group differences were observed (LA: 38% vs LC 31%; p=0.61).
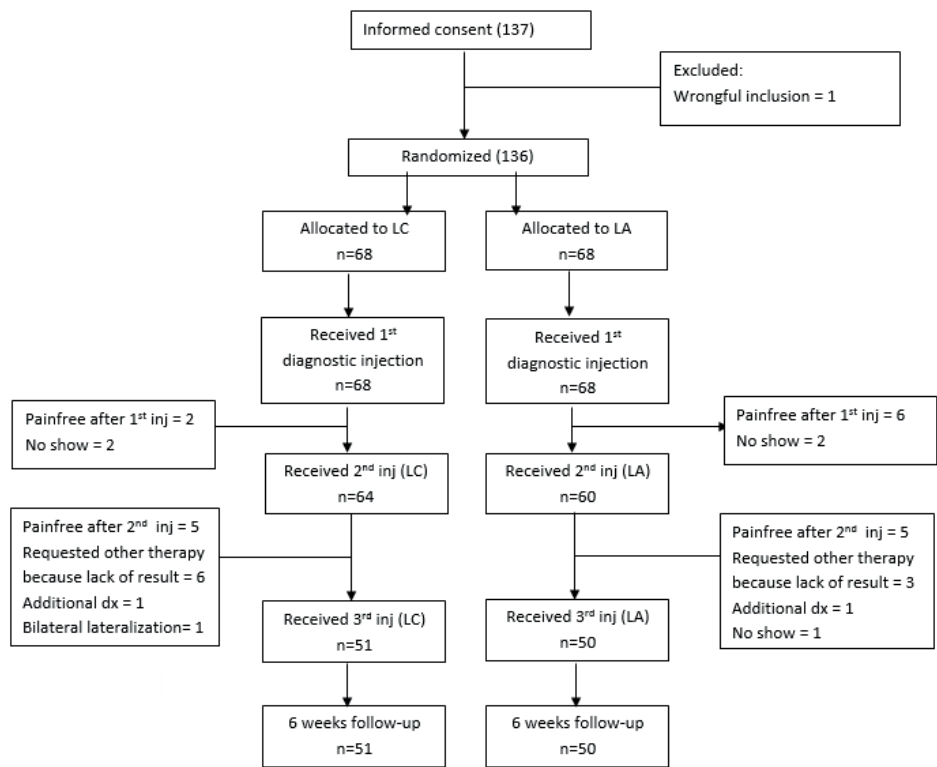
Fig. 1. Study diagram in ACNES patients receiving injection therapy using lidocaine with (LC) or without (LA) steroids.

At 12 weeks, the number of patients still experiencing pain relief was lower compared to the 6 weeks' time point (LA: 20% vs LC 18%, p=0.80) as shown in Table 2. Patients with pain recurrences between 6 and 12 weeks had undergone additional injections or pRF treatment and were excluded from this analysis.

Table 2. Primary outcome and secondary follow-up (ITT: intention to treat, PP: per protocol analysis)

	% of patients with >50% pain reduction		
Group	*6 weeks (ITT)*	*6 weeks (PP)*	*12 weeks (ITT)*
LC	34%	31%	18%
LA	43%	38%	20%

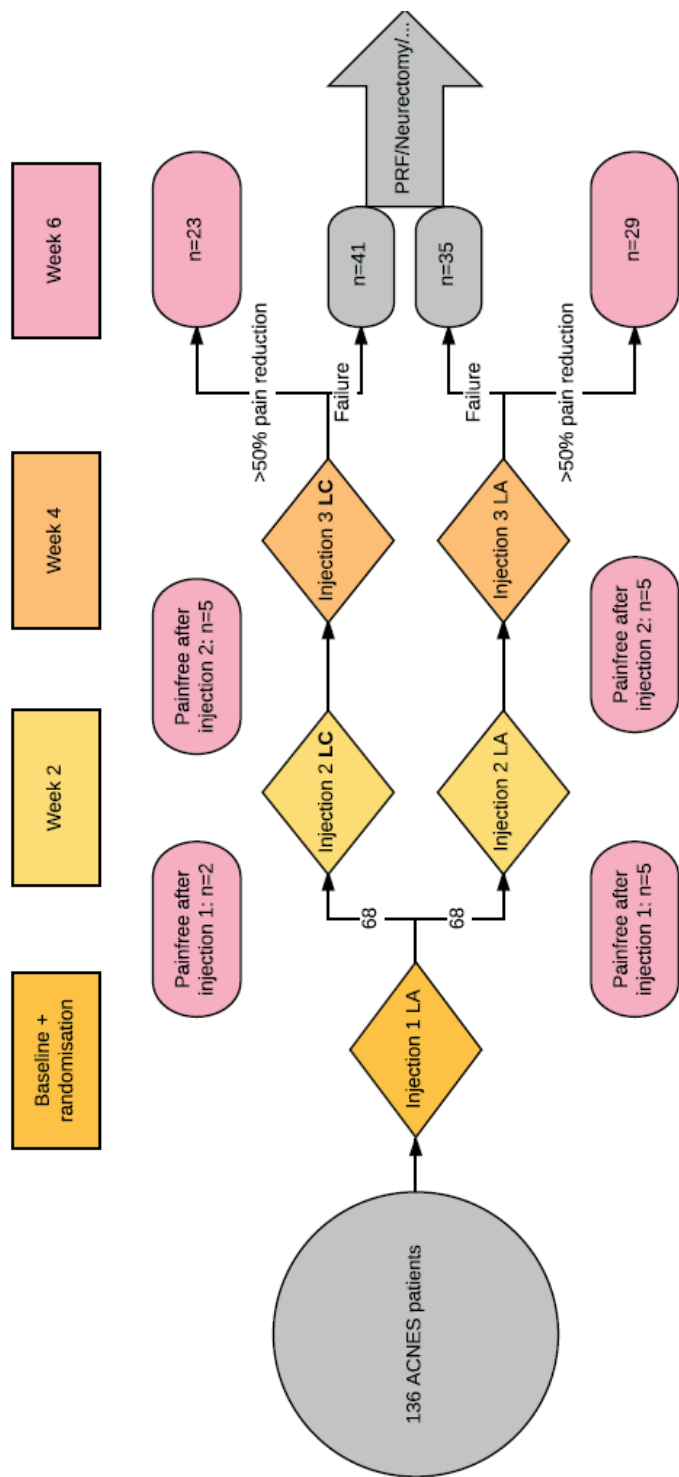$\chi2 = 1.12$, $p= 0.289$ (ITT) ; 0.49, $p= 0.48$ (PP).

Fig. 2 Effects of injection therapy for ACNES using lidocaine with (LC) or without (LA) steroids.

There were no significant differences in incidence or nature of adverse events between both groups (LA: 23/68, LC: 29/68, p = 0.46). Brief increases of pain after injection, temporary pain, tenderness or hematoma at the injection site and malaise were frequently reported. No major adverse events were observed. A multiple regression analysis including group, gender, BMI, age, duration of symptoms, baseline NRS and findings during physical examination showed no significant effect of allocated group on a successful response. A modest effect of younger age and the absence of clear somatosensory disturbances surrounding the point of maximum pain was observed (Table. 3).

Post hoc analysis

The effect of injection therapy in ACNES patients has been well established in a previous study comparing lidocaine to saline injections[3], and reduction in median pain scores in this cohort shows a clinically significant improvement from baseline NRS 7.0 to an NRS of 5.0 at 6 weeks. In designated successful responders, an average improvement of NRS 6.0 to NRS 2.0 was observed. Changes are illustrated in figure 3a and 3b. Again no significant differences present between groups.
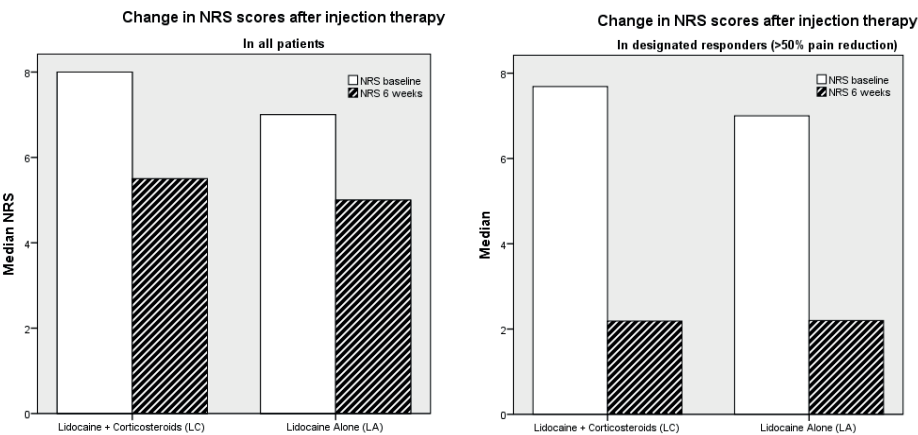

Figure 3a+b. Drop in pain level (NRS) at 6 weeks in ACNES patients following two different injection regimens in all patients (a) and designated responders (b).

Table 3. Factors predicting favorable results after injections in ACNES patients

	B (SE) [p-value]	Odds	CI 95%
Included			
Constant	*2,91(0.68)*		
Somatosensory disturbances	*-0.79(0.42)[0.059]*	*0.45*	*0.20 – 1.03*
Age	*-0.05(0.01)[0.001]*	*0.96*	*0.93 – 0.98*

R^2= 0.145 (Cox & Snell); 0.198 (Nagelkerke); Model X^2 18.65 P<0.001

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DISCUSSION

This randomized clinical trial demonstrates that corticosteroids do not exert an additional therapeutic effect in the treatment of ACNES as lidocaine alone is equally effective, both in a single and in a multiple injection regimen. The alleged systemic effect of steroids does not confer additional therapeutic success in this particular pain group as demonstrated by the median drops in NRS scores. Interestingly, the observed long term success rate of lidocaine is higher than suggested by anecdotal evidence.[18] The arbitrarily chosen regimen of 3 consecutive injections appears adequate although a substantial portion of patients required only one injection for sufficient pain relief. The intention to treat analysis that was performed therefore gives an excellent representation of clinical practice and outcomes.

A limitation of this study is the fact that a temporary successful response after a diagnostic lidocaine injection was an inclusion criterium that was deemed necessary to confirm a diagnosis of ACNES.[19] This prerequisite may possibly have preselected a subgroup of patients who would eventually also have a favorable long term response to injection therapy. Current practice in our center is that ACNES is a clinical diagnosis, and a temporary >50% pain reduction following a diagnostic block is currently not considered necessary anymore to explore treatment options other than injection therapy. A response of less than< 50% pain reduction, however, is associated with a slightly less favorable outcome after a final neurectomy procedure. [20] The authors do not expect that non-responders to a diagnostic lidocaine injection will react significantly different to the combination with steroids although caution is required. Moreover, given the fact that the outcome of the corticosteroid group was even slightly worse than the lidocaine only group, it is very unlikely that a type II error has occurred.

The overall success rate of injection therapy is comparable to findings of a previous retrospective case series of 139 ACNES patients reporting that 33% achieved >50% pain reduction after 6 weeks.[21] The lower proportion of patients who still experienced pain relief at 12 weeks strongly suggests, however, that injection therapy is only effective in a small portion of patients (1 in 5). Baseline pain scores, gender, duration of symptoms or BMI did not predict these successful patients, although younger age and lack of clear somatosensory disturbances were possibly associated with a negative outcome. Nonetheless, an 'injection therapy first approach' for each new ACNES patient is always worthwhile prior to embarking on more invasive treatments.

Remarkably, the incidence of adverse effects, although minor, was high in both groups. A substantial portion of patients (30-40%) reported increased levels of pain during the first few days following injection that typically subsided after a week. This phenomenon is possibly explained by a volume effect (5-10 ml) on surrounding tissue, or simply by burst stimulation of targeted nerves. Hematomas at the injection site occurred just oc-

casionally. Vague complaints of malaise, although less common in both groups, often coincided with this transient increase in pain suggesting either a vagal response or a systemic effect of both lidocaine and steroids as previously reported.[21]

Apart from avoiding potential side effects associated with corticosteroids injection, are there any clinical consequences of omitting these substances from the standard injection therapy for ACNES? Typical local side effects of repeated peripheral steroid injections such as subcutaneous fat necrosis and depigmentation are relatively benign but may pose a cosmetic problem, particularly in young females.[22] Moreover, abolishing steroids from the standard injection therapy in ACNES will have an impact albeit small on the cost-effectiveness of injection therapy although generic corticosteroids are fairly inexpensive.

The findings in this study will possibly contribute to a more evidence based management for pain syndromes including ACNES. A systematic review on the efficacy of perineural steroids for chronic non-cancer pain is currently underway.[23] As mentioned in their trial set up, steroids have been enthusiastically embraced for various pain conditions since their discovery in the 1940s. Because steroids were often standardly combined with lidocaine, there is just no simple way of determining which of the two agents exerts the desired beneficial effects. Lidocaine itself could possibly intervene in the vicious circle of ongoing sensitization that occurs in chronic pain, resetting the neurons' signaling properties.[24] On the other hand, steroids may possibly decrease ectopic discharge and alleviate edema surrounding injured nerves.[25,26] The pathophysiological basis underlying the type of pain syndrome will probably determine whether steroids are a valuable addition to injection therapy. For ACNES, however, the authors suggest steroids should be left out of the standard treatment regimen.

CONCLUSION

The addition of corticosteroids to an anesthetic agent for abdominal wall infiltration does not increase the proportion of ACNES patients achieving adequate pain reduction, neither on the short term (6 weeks) nor on the longer term (12 weeks). Injection therapy resulted in an overall clinically significant decrease of pain levels. Lidocaine alone can provide long term pain relief after one or multiple injections in approximately 1 of 5 patients.

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