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Comparing Collagenase and Tissue Subcision for Cellulite Treatment of the Buttock and Thigh Regions: A Systematic Review and Meta-analysis

Jose A. Foppiani, MD*†
Otakar Raska, MUDr, PhD†
Cécilia Galinaud†
Stephen Stearns, BS*
Angelica Hernandez Alvarez, MD*
Iulianna C. Taritsa, BA*
Kirsten A. Schuster, MD, JD*
Olivia A. Ho, MD, MMSc, MPH‡
Sarvam TerKonda, MD‡
Bernard T. Lee, MD, MBA, MPH*
Samuel J. Lin, MD, MBA*

Background: In this systematic review, we assessed the therapeutic efficacy and safety of *Clostridium histolyticum* collagenase (CCH) and tissue subcision (TS) for treating cellulite, which ranges from subtle to pronounced lesions.
Methods: A systematic review was performed following PRISMA guidelines for CCH and TS treatment to the thigh and gluteal regions. A proportion meta-analysis was then conducted using Stata statistical software.
Results: A total of 14 studies were incorporated into the final analysis. Nine focused on TS and five on CCH injection, collectively reporting outcomes for 1254 patients. Of these, 465 received CCH injection and 789 underwent subcision. For bruising, rates were 89% [95% confidence interval (CI), 71%–96%] with CCH injection and 99% (95% CI, 85%–99%) for subcision; pain requiring analgesic was reported at 74% (95% CI, 55%–87%) for CCH and 60% (95% CI, 43%–76%) for subcision; both showed induration at 7% (95% CI, 5%–11% for CCH, 95% CI, 2%–25% for subcision), whereas skin discoloration was higher post-CCH injection at 16% (95% CI, 10%–26%) compared with 7% (95% CI, 5%–10%) postsubcision.
Conclusions: Both CCH and TS seem effective treatments for cellulite. However, upon evaluating the adverse outcomes between the two modalities, subcision demonstrated a higher incidence of bruising, albeit similar rates of induration compared with CCH injection. Conversely, the CCH injection group manifested a higher propensity for pain requiring analgesia and notably exhibited increased instances of skin discoloration compared with their subcision patient group. Further standardized research is crucial for more informed cellulite treatment decisions and for comparing efficacy, safety, and cost-effectiveness between TS and CCH.
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INTRODUCTION

Cellulite, a condition precipitated by both regressive and progressive structural alterations of the skin, is characterized by subcutaneous adipose tissue lobes interspersed with fibrous septa.[1,2] The tethering of superficial skin to underlying fat lobules by fibrous cords results in pressure against the dermis and the subsequent manifestation of macroscopically discernible dimpling.[1] These changes can range from nearly imperceptible to markedly visible and painful lesions which often have distressing psychosocial implications for affected individuals.[3] Although extensive research has been conducted, the pathogenesis of cellulite remains elusive, with potential contributing factors encompassing hormonal imbalances, subcutaneous fat deposition, vascular alterations, and inflammatory mediators.[3,4] Cellulite typically starts during early adolescence and may be exacerbated during pregnancy or menopause, posing a significant cosmetic and social challenge for the 80%–98% of individuals affected.[4,5] Interventions targeting fibrous septa have shown partial success in managing

*From the *Division of Plastic Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass.; †Department of Pathophysiology, Universita Karlova, Prague, Czech Republic; and ‡Division of Plastic Surgery, Mayo Clinic, Jacksonville, Fla.*

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cellulite, including laser and light modalities combined with radiofrequency, acoustic wave therapy, tissue subcision (TS; a minimally invasive procedure involving manual disruption of fibrous cords), and enzymatic therapies.[6]

The enigmatic pathophysiology of cellulite has historically rendered its treatment complex due to the multitude of potential targets.[1] The macroscopic presentation of cellulite is hypothesized to be influenced by fibrous septa characteristics (thickness and organization), dermal support for underlying layers, and the architecture of deep and superficial fat layers.[7] Surgical subcision devices such as Avéli (Revelle Aesthetics, Inc., Mountain View, Calif.) and Cellfina (Merz North America, Inc., Raleigh, N.C.), with their capacity to directly target fibrous septa, emerged as a prevalent treatment modality for cellulite; however, concerns persist regarding its invasiveness, inconsistent results, and associated morbidity.[7,8] Consequently, more precise and less invasive treatment alternatives have been developed, such as collagenase *Clostridium histolyticum*-aaes (CCH-aaes), with products such as Qwo (Endo International plc., Malvern, Pa.) rising in popularity.[9] Despite the diverse array and rapid advancements in potential cellulite treatments, particularly for the buttock and thigh regions, direct comparisons between TS and enzymatic treatment using CCH-aase injections are lacking. Thus, this meta-analysis aims to evaluate the efficacy and safety of collagenase-producing CCH and TS in the management of cellulite.

Takeaways

Question: How effective and safe are collagenase-producing *Clostridium histolyticum* (CCH) compared with tissue subcision (TS) in the management of cellulite?

Findings: In a meta-analysis of 14 studies with 1254 patients comparing TS and collagenase-producing CCH for cellulite, CCH showed higher rates of bruising and skin discoloration, whereas pain requiring analgesics was higher in TS.

Meaning: Patients considering CCH for cellulite treatment should be aware of the higher risk of bruising. Companies must address this issue to make CCH as marketable and effective as TS.

METHODS

This study protocol was prospectively registered with PROSPERO (Study no. ID: CRD 42023395119).[10] This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.[11]

Eligibility Criteria

Criteria for included studies were defined as male or female patients 18 years or older who have received treatment for cellulite (with either CCH or TS methods) to the buttock or thighs regions for aesthetic purposes. (**See table, Supplemental Digital Content 1**, which displays the inclusion and exclusion criteria, **http://links.lww.com/PRSGO/D251**.) The full eligibility criteria accessible at PROSPERO.[10]

Search Strategy

This systematic review follows the PRISMA guidelines.[11] A comprehensive research review using subject headings, controlled vocabulary and keywords was used to search on Ovid/MEDLINE, Embase, Web of Science, and the Cochrane Central Register, ClinicalTrials.gov. co for studies published until 2023. The search was performed by an experienced medical librarian.

Study Selection

The search results were uploaded to Covidence.[12] A two-stage screening process was conducted for study selection. Two screeners independently reviewed the titles and abstracts in the first step. When discordances were present, a third reviewer made the final decision on the inclusion of a study. In the second stage, the same two reviewers performed a full-text review and selected studies that fulfilled the eligibility criteria. When discordances were present, a third reviewer made the final decision on the inclusion of a study.

Data Extraction/Synthesis

Data extraction was guided by the following predetermined checklist: first author last name, year of publication, total sample size and control group size, gender, mean age, CCHs versus TS, follow-up duration, outcome of interest, area of injection, injection technique or device, outcomes reporting scale, technique for product processing/preparation, preoperative baseline assessment, patient satisfaction, and adverse effects.

Outcomes

The primary outcome was patient-reported outcomes, including, but not limited to, the quantitative (average decrease in cellulite after treatment) and qualitative results (satisfaction with treatment and results). Secondary outcomes were the reported complication rates and adverse events.

Quality Assessment

The National Institute of Health study assessment quality tool was used to evaluate the selected articles.[13] Each article was categorized as follows: "good," "fair," or "poor."

Statistical Analysis

A comprehensive qualitative analysis was made. For the quantitative analysis, the binomial data were analyzed. Each complication rate's pooled prevalence was estimated using a proportion meta-analysis with Stata statistical software (version 16.1, STATA Corp., College Station, Tex.).[14] The highest count of a given adverse effect within the follow-up of 30 days was recorded and served as the data for the meta-analysis. Due to the heterogeneity among studies, a logistic-normal-random-effect model was conducted. Ninety-five percent exact confidence interval (CIs) and 95% Walds CIs were performed for study-specific and

overall pooled prevalence, respectively. Additionally, the Freeman–Tukey double arcsine transformation was used. The percentage of weight and effect size of each study were presented.[15] To assess heterogeneity, I^2 statistics was used. Significant heterogeneity was considered at a P value of less than 0.05 or I^2 greater than 50%.

RESULTS

Study and Participant Characteristics

A total of 897 studies were identified during the initial screening process. After exclusion of duplicates and manual review against established criteria, 14 studies were included in the final analysis, with nine describing mechanical TS[16–24] and the remaining five describing CCH injection[6,25–28] (Fig. 1). (**See table, Supplemental Digital Content 2**, which displays the Food & Drug Administration approval of devices and products included for analysis, **http://links.lww.com/PRSGO/D252**.)

Included articles were published between 2000 and 2022. A summary description of each is detailed below with NIH Quality Assessments determined for each and compiled in Supplemental Digital Content 3. (**See table, Supplemental Digital Content 3**, which displays the summary characteristics and findings of included studies, **http://links.lww.com/PRSGO/D253**.) These studies described the outcomes of 1254 patients, 465 who received CCH injection and 789 who received TS interventions for cellulite. The average patient in the CCH cohort was 46.6 years old versus 39.3 in the TS group. The thigh was the location of interest in all studies, with 13 (92.9%) examining the cellulite on the buttock as well.

Treatment Protocol

Subcision protocols are still evolving and improving with each clinical trial. We conducted a comparison of the different techniques, procedures, and pre- and postoperative protocols for each method, separating the

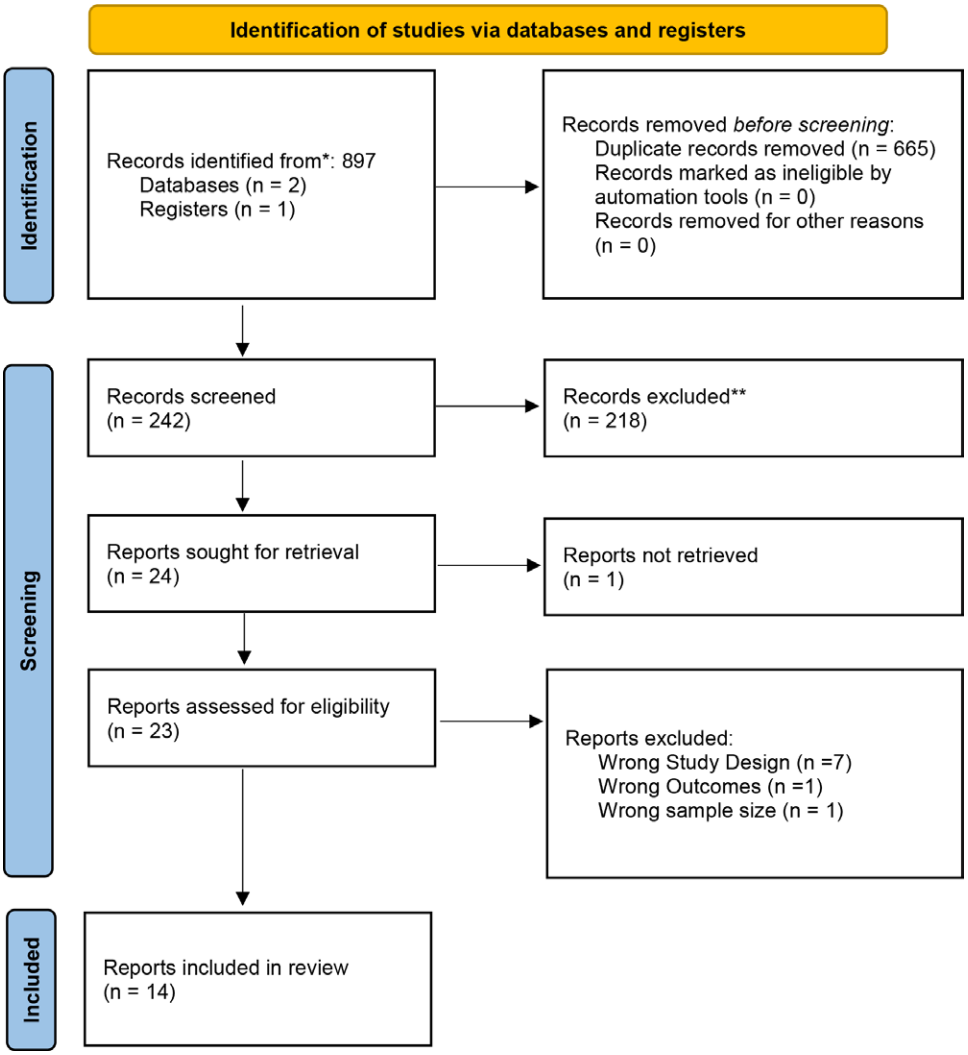

Fig. 1. Systematic reviews and meta-analysis (PRISMA) guidelines flow diagram. *Records obtained by our librarian. **Records excluded manually.

CCH subcision in Table 1 and mechanical subcision in Supplemental Digital Content 4. (**See table, Supplemental Digital Content 4,** which displays the TS treatment: application techniques and postoperative treatment, **http://links.lww.com/PRSGO/D254**.)

From Supplemental Digital Content 4 (**http://links.lww.com/PRSGO/D254**), it is evident that the treatment protocol in CCH studies is inconsistent because the search for an optimal treatment protocol is still ongoing. Despite this lack of uniformity, some trends are apparent, and most CCH trials used a similarly constructed treatment method. The treatment region was selected before the procedure, usually when the patient was standing and relaxed, by marking well-defined and evident cellulite dimpled areas. With the exception of Bhatia et al,[25] CCH treatment was administered in 3 (or up to 3) separate treatment sessions.[6,26–28] This finding contrasts with the TS method requiring only 1 session for treatment, as seen in Supplemental Digital Content 4 (**http://links.lww.com/PRSGO/D254**). The CCH treatment was usually administered subcutaneously, though it varied with regard to number of injections, frequently 12, and dose injected, with 0.84 mg being the most frequent total or highest dose.[6,25–28] Each study used a different injection strength or total administered dose, with one trial even including a placebo.[6,25–29] The angle of injections was mainly an alternation between a right angle and a 30- to 45-degree angle to the skin. Only the study by Joseph et al[26] reported a preoperative treatment with a local anesthesia and deep sedation protocol.[6,25,27,28] No special recommendation for the postoperative treatment was reported, with the exception of a sterile dressing application for 1 day if necessary[29] and a possible compression garment after injection and after each treatment session.[6,25–28]

This finding contrasts with the TS method that reported more recommended pre- and postoperative treatments and procedures in an attempt to decrease the rate of common adverse events, as shown in Table 2. Mechanical subcision treatments have been used in plastic surgery for longer than the CCH treatments. This explains the great array of methods, techniques, devices, and procedures used in our nine TS studies, as reported in Supplemental Digital Content 4 (**http://links.lww.com/PRSGO/D254**).

Table 1. *Clostridium histolyticum* Collagenase Application Techniques and Postoperative Treatment

Author	Treatment Sessions	Preoperative Treatment	Treatment Area Selection	Area of Injection	Dose Injected	Injection Technique	Postoperative Treatment
Sadick et al[29]	Up to 3	N/A	Visible and well-defined dimples when patients were in a relaxed, standing position	One buttock or thigh randomly assigned	0.84 mg as 12 s.c. injections or placebo	3×0.1 mL aliquots applied: approximately 2 cm apart, one aliquot perpendicular to the skin, 2 aliquots at a 45-degree angle to the left or right of the perpendicular axis	A sterile dressing to the injection site if necessary, Patients were directed to remove the dressing that evening
Bhatia et al[25]	1	N/A	N/A	Thigh or buttock	Injection per area: 12 s.c injections, 0.84 mg dose 1 area: thigh or buttock (total 0.84 mg) OR 2 areas: thigh or buttock (total: 1.68 mg) OR 4 areas: right and left thigh; right and left buttock (total: 3.36 mg)	3×0.1 mL aliquots applied: 1 aliquot perpendicular to the skin, 2 aliquots at a 45-degree angle to the left or right of the perpendicular axis, 2 cm apart if more than 1 injection needed per dimple	N/A
Kaufman-Janette et al[27]	3	N/A	N/A	Each of the 2 buttock or 2 thigh treatment areas	0.84 mg as 12 s.c. injections, total dose of 1.68 mg and 24 injections	3×0.1 mL aliquots applied:1 aliquot perpendicular to the skin, 2 aliquots at a 45-degree angle to the left or right of the perpendicular axis, ½ inch in depth	N/A
Joseph et al[26]	Up to 3	Local anesthesia + deep sedation	Visible and well-defined dimples when the patients were standing; up to 12 dimples per treatment area were selected	Thigh	Up to 0.84 mg (18 mL) of CCH-aaes was administered subcutaneously, with the patient in the prone position, in up to 12 dimples	5×0.5 mL aliquots applied, at a 30-degree angle to the skin, one 1 inch in depth, four ½ in depth	Use of a compression garment after injection was allowed after each treatment session
Goldman et al [29]	Up to 3	N/A	Well-defined, evident cellulite dimples	Posterior thigh or buttock	Low (0.06 mg), mid (0.48 mg), or high-dose (0.84 mg) CCH	N/A	N/A

N/A, not applicable.

Table 2. Summary of Reported Adverse TS versus CCH Method

Treatment	Average No. Adverse Events per Subject*	No. Studies Providing Adverse Event Data	Average No. Serious Adverse Events and Adverse Events Leading to Discontinuation per Subject*	No. Studies Providing Discontinuing/Serious Adverse Event Data
TS	1.8	7	0	0
CCH	2	4	0.01†	1

*Studies that did not provide data regarding this (N/A) were excluded from the calculation.
†One study with 63 patients reported two adverse events that led to discontinuation, which represents 0.01 patients with severe adverse events for every patient without said events in all of the reporting studies.

No matter the method used, only one treatment session was required for mechanical subcision, contrasting with the CCH treatment generally requiring three (Table 1).[16–24] The TS-GS or Cellfina system was the treatment method of choice in six of our nine mechanical subcision papers, making it the most studied device of all the methods described in our systematic review (Brauer et al).[16–25] Almost all studies, independent of the method used, recommended wearing a compression garment or another type of compressive clothing for an average of 14 days after the procedure. Postoperative compression was the most consistent recommendation across methods. Amore et al[22] using the CelluErase device had the longest postoperative compression treatment recommendation (1 month) in addition to multiple lymphatic drainage or pressure therapy sessions.[16–24] The minimally invasive targeted verifiable subcision using the Avéli device as described by Stevens et al[23] was the only study that did not recommend compression therapy of any kind, which might be explained by a lesser amount of skin incision necessary.[16–22,24]

Efficacy

Our findings show generally positive results across all studies, although variations in assessment methods, patient sample sizes, and satisfaction reporting scales limit our ability to definitively determine which technique is superior. (**See table, Supplemental Digital Content 5**, which displays the summary of patient's reported satisfaction, **http://links.lww.com/PRSGO/D255**.)

The Investigator Global Aesthetic Improvement Scale was the most frequently used, featured in seven of our 14 studies.[6,16–27,29,31] This clinician-based evaluation measures cellulite appearance changes using before and after images. Similarly, the Subject Global Aesthetic Improvement Scale was used in five studies and used patient feedback. Although subjective, these scales predominantly indicated improvement. For instance, the CCH study by Sadick et al[29] reported more than 60% investigator and 70% patient satisfaction.[6,16–27,29,31] The Cellulite Severity Score was used in four studies, whereas others used unique systems such as the Clinician-reported Photonumeric Cellulite Severity Scale and the Patient-reported Photonumeric Cellulite Severity Scale. An additional five studies reported on arbitrary patient satisfaction scales. Furthermore, only one study evaluated the psychological impact of the treatment on aspects such as clothing choices.[6,16–27,29,31]

Safety Profile

The safety comparison attempted to evaluate the frequency of commonly reported side effects. Twelve of our 14 studies were included in our statistical (quantitative) analysis; two studies (Goldman et al, 2015; Kamimer et al, 2019) could not be included as they did not report the relevant data.[6,16–26,28–32]

Meta-analysis of the various side effects of each treatment were compared if at least two studies per intervention subgroup quantified a given side effect, to ensure more robust comparison. Rates of bruising [CCH injection: 89% (95% CI, 71%–96%), subcision: 99% (95% CI, 85%–99%), Fig. 2], pain requiring analgesic [CCH injection: 74% (95% CI, 55%–87%), subcision: 60% (95% CI, 43%–76%), Fig. 3], and induration [CCH injection: 7% (95% CI, 5%–11%), subcision: 7% (95% CI, 2%–25%), Fig. 4] failed to demonstrate significant differences between intervention types. Skin discoloration was more frequently reported after CCH injection than after subcision [16% (95% CI, 10%–26%) versus 7% (95% CI, 5%–10%), respectively, Fig. 5).

DISCUSSION

The elusive nature of cellulite pathogenesis has resulted in a wide range of clinical therapeutic approaches aimed at improving the cosmetic appearance of all areas where cellulite may precipitate.[33] Given this plethora of overlapping information and approaches, there is clear value in attempting to form consensus on the relative efficacy and safety of contemporary cellulite treatment approaches. In this systematic review, we focus on the management of thigh and buttocks cellulite, with TS and CCH collagenase protocols. No previous comprehensive comparison of these two modalities in terms of their effectiveness and safety exists.

From the data tables, distinct differences emerge in the safety profiles of the CCH and TS treatments for cellulite. Adverse events seem more prevalent with CCH, implying a marginally better risk profile for TS, although it is essential to note that neither method produced severe complications in our cohort, attesting to the general safety of both approaches. Subcision, although recognized for its efficacy, manifested a notably higher bruising incidence at 99% (95% CI, 85%–99%), compared with CCH's 89% (95% CI, 71%–96%). This prevalence, although slightly higher than CCH, is consistent with historical data, underscoring the persistent challenge of bruising across cellulite treatments over the years. Indeed, a review by Dadkhahfar et al[34] reported up to a 90% bruising rate after TS procedures. This review, which includes studies conducted more than 20 years ago showcasing a similar rate to our study, reveals that local complications of the treatment of cellulite have

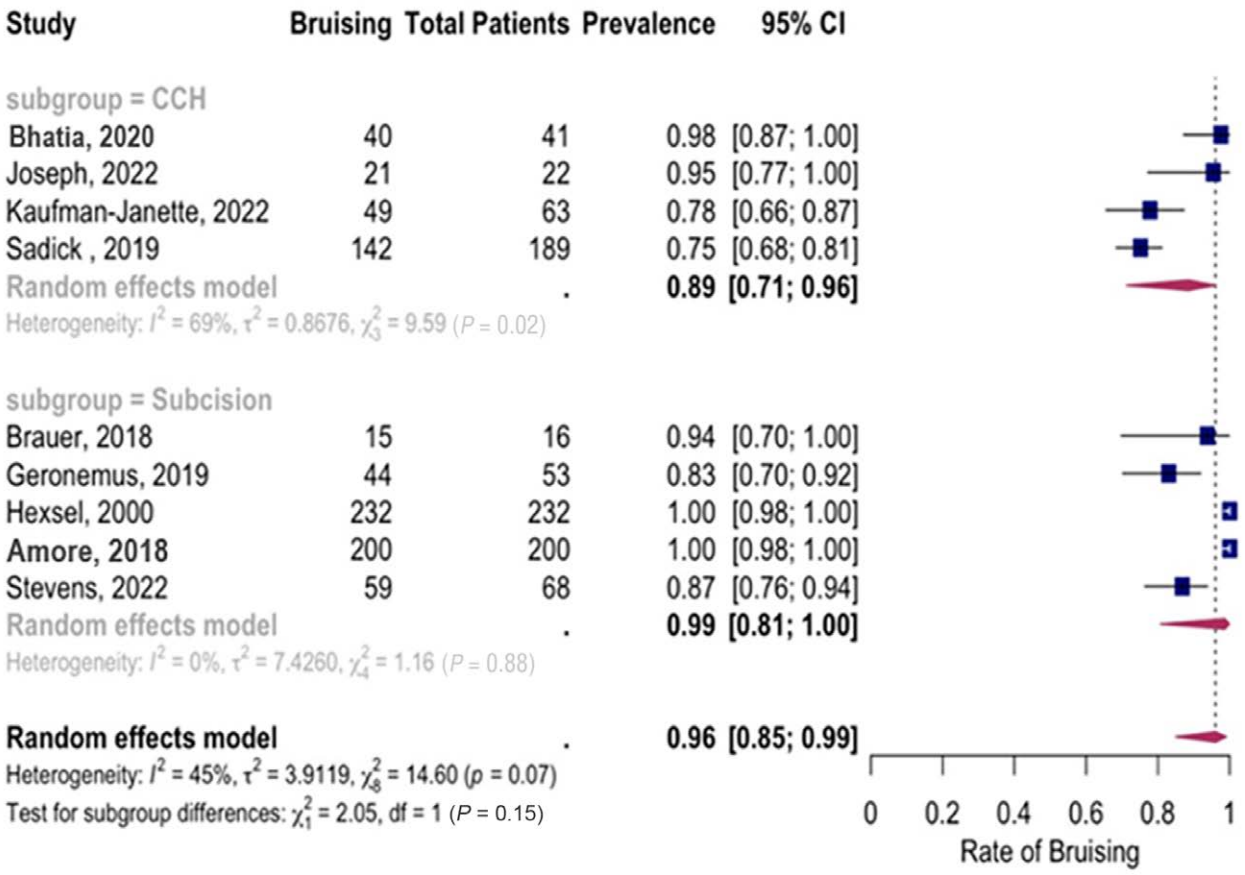

Fig. 2. Side effects of the CCH injection vs TS—bruising by intervention.

not improved despite newer techniques and modality introduction.

On the other hand, pain postprocedure seemed more associated with CCH, where 74% (95% CI, 55%–87%) required analgesics, in contrast to the 60% (95% CI, 43%–76%) for subcision. This indicates a possible trade-off between bruising and pain for the two treatments, suggesting that patient preference might lean towards one based on individual pain tolerance and aesthetic considerations. Interestingly, both modalities showcased almost parallel rates of induration. Skin discoloration, however, marked a significant point of differentiation. CCH procedures resulted in a higher 16% (95% CI, 10%–26%) rate, nearly double the 7% (95% CI, 5%–10%) observed with subcision. Considering the overarching data, it is evident that although both CCH and TS are valuable treatments in the arsenal against cellulite, their divergent side effect profiles make them suited to different patient priorities. The heightened bruising with subcision might deter some, whereas the increased pain and skin discoloration with CCH could be a concern for others. Given these insights, prospective patients would greatly benefit from a comprehensive understanding of these nuances to make informed treatment choices. Moreover, the medical community stands to gain from further research, sharpening the comparative lens on efficacy, safety, and cost-effectiveness of TS and CCH, and potentially refining these treatments for better patient outcomes.

Unfortunately, there was limited overlap in the scales used by the investigators to assess improvement and patient satisfaction between the CCH and TS groups, making it challenging to establish a common basis for analysis. This lack of standardization and the uneven proportion of the study count in each treatment category prevented quantitative comparisons of effectiveness of TS and CCH procedures and, thus, drawing any definitive conclusion on the superiority of any of these methods. The need for a standardized approach to the scoring of cellulite severity and the impact of its treatment has been discussed by Young and DiBernardo.[35] Currently, the clinician and patient-reported photograph-numeric cellulite severity scale (PCSS) and the digital photography evaluation have been deemed the most comprehensive, validated, and reliable methods for assessing the cellulite severity because they are simple to use, and the PCSS also enables the inclusion of patients' opinions on the treatment they received.[35] Of note, only two studies within our review used the PCSS and digital photography evaluation.[6,17,30] Despite these limitations, the outcome of both procedures seems comparable.

Other modalities used in the treatment of cellulite, as well as other aesthetic targets treated with subcision

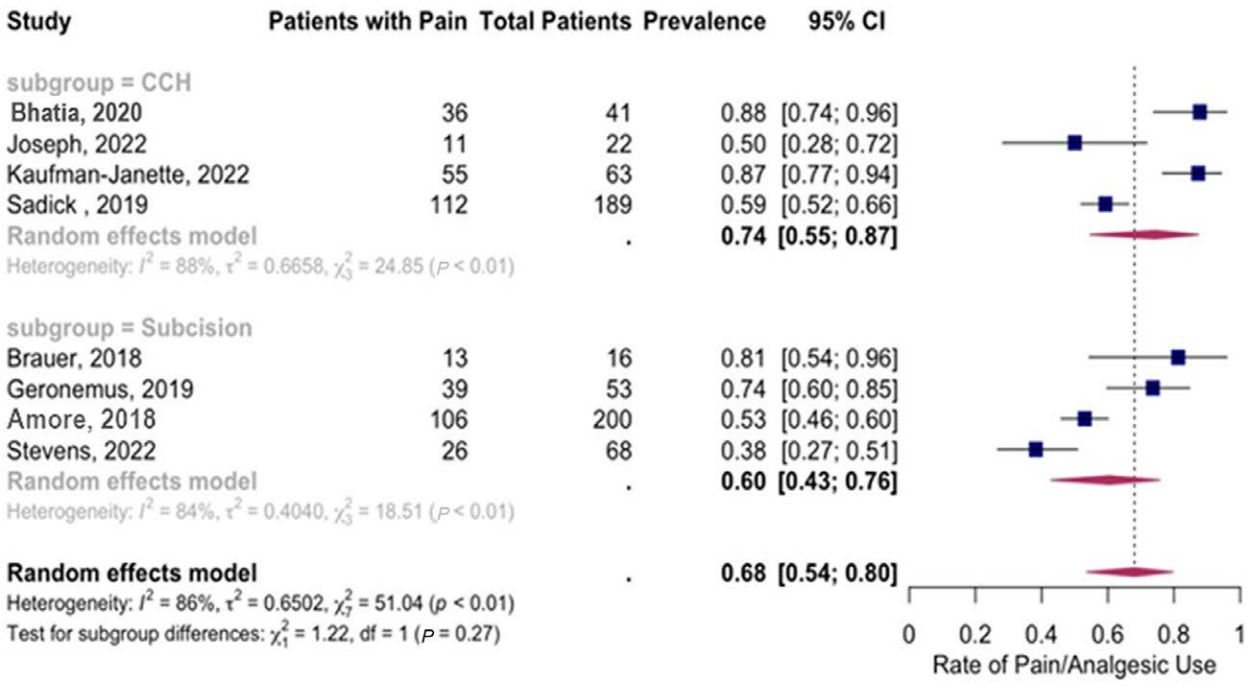

Fig. 3. Side effects of the CCH injection vs TS—pain requiring analgesic use by intervention.

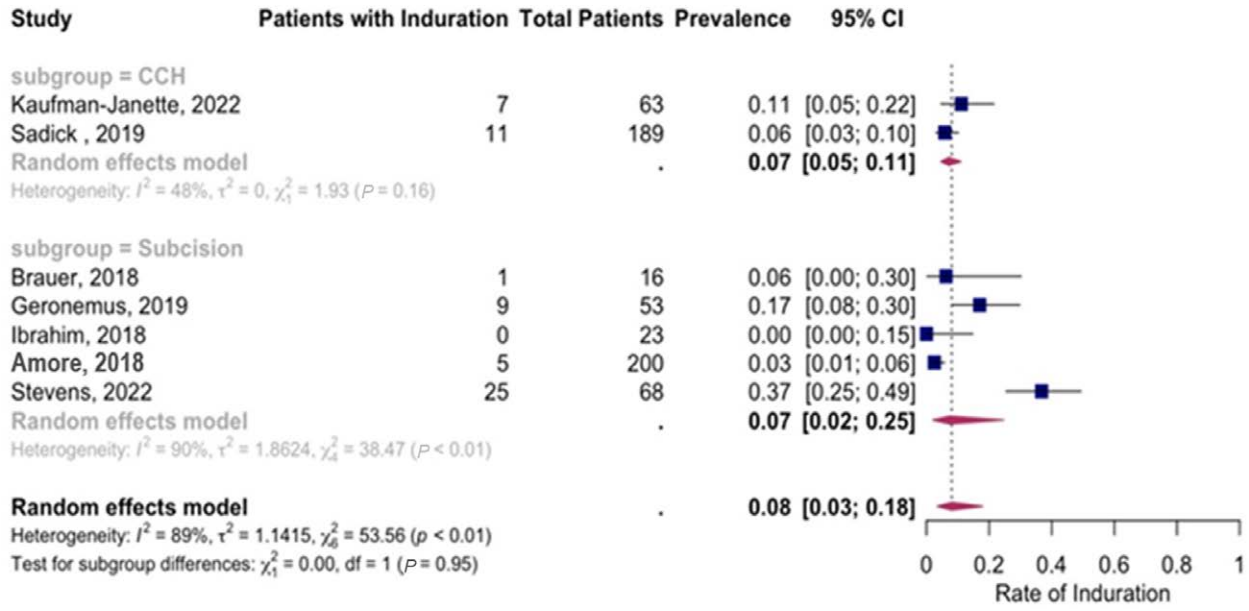

Fig. 4. Side effects of the CCH injection vs TS—induration by intervention.

or CCH collagenase (atrophic scars, Duputryen, and Peyronie contracture), seem to be facing similar difficulties in terms of the reporting quality and finding a unifying measure to assess the outcome.[36–41] Turati et al[36] criticized the lack of appropriate reporting regarding the sample size calculations, statistical methods, the number of participants, and their characteristics. Nevertheless, they evaluated the efficacy of cosmetic products on cellulite by evaluating the thigh circumference change.[20] A review of extracorporeal shock wave therapy showed various outcome measures used in the included studies.[37] Meta-analyses repeatedly pointed to the heterogeneity of outcomes, leading to the inability of direct comparisons among the studies, or preventing the investigators from conducting more robust analyses and drawing more reliable conclusions due to a low count of studies that could be included in the quantitative synthesis.[36–41]

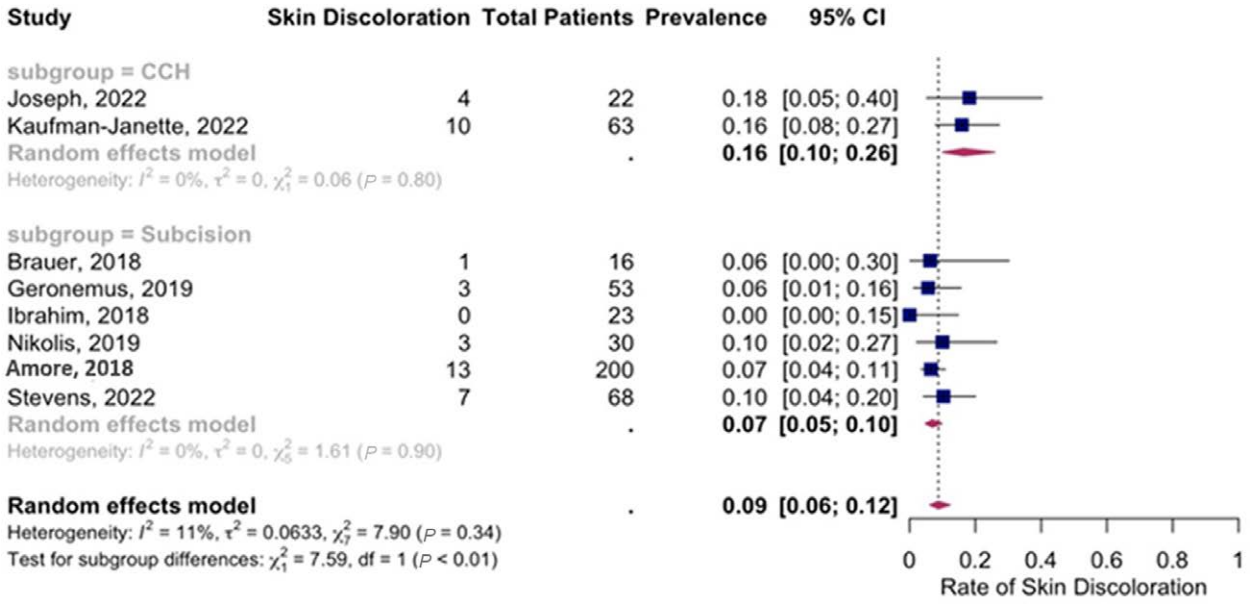

Fig. 5. Side effects of the CCH injection vs TS—discoloration by intervention.

LIMITATIONS

This study has its limitations. Differences in the scales used by investigators to assess improvement and patient satisfaction limited the common basis for analysis. This lack of standardization and the uneven proportion of the study count in each treatment category prevented us from quantitatively comparing the effectiveness of TS and CCH procedures and, thus, drawing any definitive conclusion on the superiority of any of these methods. Although we tried to even out the effect of variably long follow-up periods on the adverse effect reporting by setting a limit of 30 days, different average times of follow-up in the TS and collagenase categories (419 versus 53 d) made it difficult to compare long-term adverse effects. Simultaneously, this limitation could affect satisfaction reporting as well. The subjective nature of several steps in some studies is another major drawback. Both the selection of the area of treatment and the extent of the procedure, either tissue release or the amount of collagenase applied, was determined by the operating surgeon individually for each patient. These limitations are not inherent to this review but to reviews looking at the treatment of cellulite regardless of the modality chosen, pointing out a significant flaw in how studies are conducted in this field. Efforts must be directed toward standardizing the reporting of patient demographics, characteristics, intervention effectiveness, patient satisfaction, and adverse effects. This standardization is essential for enabling the objective comparison of results across studies. Finally, it is crucial to recognize that although Cellfina and Avéli are both utilized for targeting septa in TS, the devices and methodologies used in their usage are distinct. This differentiation warrants further investigation, particularly in comparative analyses of their respective efficacies and outcomes.

CONCLUSIONS

From this meta-analysis, both CCH and TS have emerged as potentially effective treatments for cellulite in the thigh and buttock regions. Each method offers a distinct approach to cellulite management, characterized by its own procedural mechanics and tissue responses. Delving into clinical nuances reveals significant differentiators. For instance, TS, although effective, often results in a higher incidence of bruising. Conversely, treatments involving CCH are typically associated with increased postoperative pain, necessitating analgesics, and a notable prevalence of skin discoloration. These divergent outcomes underscore the variability in treatment responses and highlight areas requiring further refinement. Future research, focusing on standardizing procedural specifics, patient experiences, and associated costs, will be instrumental in more effectively comparing these treatment outcomes.

Samuel J. Lin, MD, MBA
Department of Surgery
Division of Plastic and Reconstructive Surgery
Harvard University
110 Francis St, Suite 5A
Boston, MA 02215
E-mail: sjlin@bidmc.harvard.edu

DISCLOSURES

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