



Title	Effectiveness and adverse effect of cryolipolysis in fat reduction : systemic review
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Abstract of Project entitled

“Effectiveness and adverse effect of cryolipolysis in fat reduction: Systemic review”

Submitted by

Yau, Ching Tsz

for the Degree of Master of Public Health

at The University of Hong Kong

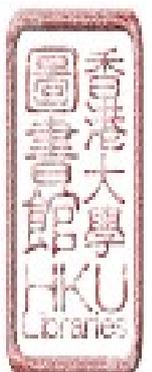
in August 2015

Background/Objective:

Obesity becomes an important issue in public health nowadays. The prevalence and incidence of obesity are in upward trend, which posts great burden of morbidity and mortality to the community. Obesity causes various complications leading not only to huge economic burden in medical sector and the community, but also to the individual family. Apart from the mainstay of weight management including healthy lifestyle (i.e. healthy dietary practice and regular physical workout), people try various methods to achieve weight loss. There are many cosmetic procedures claimed to be effective to serve this purpose, liposuction is believed to be the most popular procedure in fat reduction. However, we noted news about death and other complications reported after received liposuction procedures in recent years. Regarding new advance, cryolipolysis is a new and noninvasive technique, claimed to be effective even in single treatment and safe, to reduce body fat especially localized fat. If supporting evidences are valid, people may have safer choice of fat reduction in terms of cosmetic procedures.

Methods:

A systemic review was performed by literature searching from various database including PubMed, Google Scholar, Google and Yahoo for the effectiveness and adverse effects of cryolipolysis in fat reduction to select the relevant Journals and articles in English that talk about the theme up to



2015.

Results/Findings:

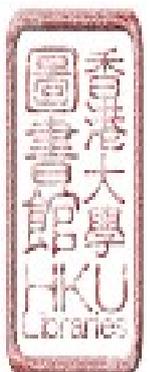
In this study, all articles identified in available database were included for review. A total of 14 relevant studies, consisting 12 case-control studies and 2 retrospective studies, were included in this review. Overall, cryolipolysis is effective in fat reduction with tolerable side effect, and no long lasting skin problem or nerve damage was reported.

Conclusions:

The increasing popularity of the cosmetic procedure nowadays poses public concern on the effectiveness and safety of the procedures. This project reviewed the effectiveness and adverse effect of the noninvasive procedure cryolipolysis in fat reduction. All preclinical and clinical trials showed promising effects but the sample sizes in the trials identified were small, and only short follow-up period of the outcome and adverse effect after the procedure. In this regards, a further large scale case control study should be performed in future to confirm the effectiveness and adverse effect of cryolipolysis in fat reduction. Nevertheless, healthy lifestyle including healthy eating and regular physical workout remains the mainstay of intervention in combating obesity and should be emphasized in public health education.

Keywords: Cryolipolysis, coolsculpting, noninvasive fat reduction, body contouring, new advance in fat reduction

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Effectiveness and adverse effect of cryolipolysis in fat reduction: Systemic review

by

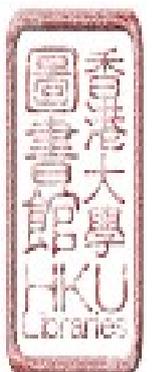
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Supervisor: Dr. Dennis IP

A Project submitted in partial fulfilment of the requirements for
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at The University of Hong Kong.

August 2015

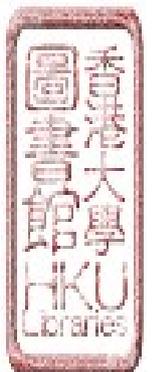


Declaration

I declare that this Project represents my own work, except where due acknowledgement is made, and that it has not been previously included in a thesis, dissertation or report submitted to this University or to any other institution for a degree, diploma or other qualifications.

Signed _____

Yau, Ching Tsz



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Heartfelt thanks to Dr. Dennis IP for his valuable advice and continuous support on this Project. Dr. IP gave me guidance and constructive advice all along. Thank you so much indeed to Dr. IP for his kindness.

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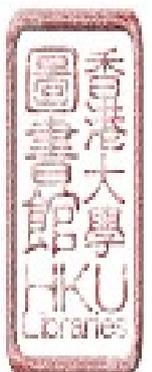
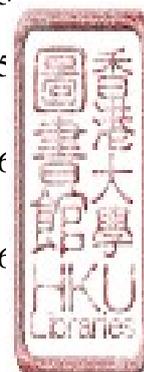
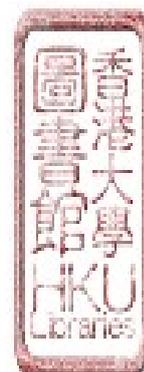


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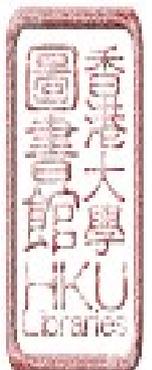
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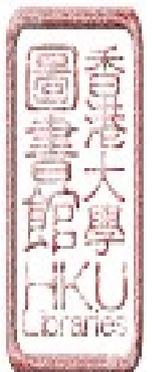
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List of Abbreviations

BMI	Body Mass Index
CDC	Centres for Disease Control and Prevention, United States
CT	Computer tomography
DH	Department of Health, Hong Kong
FDA	Food and Drug Administration
HE	Histology Examination
NCD	Non-communicable diseases
PAH	Paradoxical adipose hyperplasia
QST	Quantitative sensory testing
US	United States
USG	Ultrasound
WHO	World Health Organization
3DP	Three dimensional photography
5psQ	5-point scale questionnaires



Chapter 1 – Background

1.1 Diagnosis of obesity

According to World Health Organization (WHO), obesity is defined as Body Mass Index (BMI) 30 or above[1]. BMI is the most useful and common population level measurement for obesity as it is same for both sexes and for all ages of adults and can be calculated by a formula [BMI= Weight (kg) /Height (m) x Height (m)][1]. It is a rough assessment and may not reflect the degree of fatness. According to Centres for Disease Control and Prevention (CDC), United States, the reference of BMI for Caucasian adults is suggested as below table 1[2].

Table 1: BMI reference for Caucasian adults

BMI = Weight (kg) /Height (m) x Height (m)	Considered
Below 18.5	Underweight
18.5 to 24.9	Normal
25.0 to 29.9	Overweight
30 or above	Obese

For Asian, the definition of obesity is a bit different. According to Department of Health, Hong Kong, (DH), the BMI was calculated by the same formula and the reference range is suggested as below table 2 [3].

Table 2: BMI reference for Asian adults

BMI = Weight (kg) /Height (m) x Height (m)	Considered
Below 18.5	Underweight
18.5 - 22.9	Normal
23 - 24.9	Overweight
25 or above	Obese



1.2 Epidemiology of obesity

Obesity is getting doubled globally since 1980 according to statistics provided by WHO. In 2014, more than 600 million adults worldwide were obese, corresponding to 13% of adults population[1]. Besides, near 40% of adults were overweight in 2014[1]. Hence, more than half population is not in the range of normal body weight. In United States (US), the situation is even worse, over 30% of US adults are obese according to statistics provided by CDC[4].

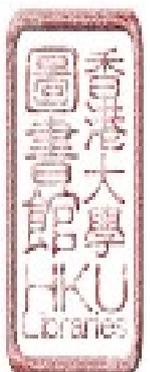
Regarding the local condition in Hong Kong, with reference to a local survey performed by Department of Health, 18.8% of adults in Hong Kong were obese in 2012 in compare to more than 20% in previous years[5]. The situation in Hong Kong is similar or slightly lower in recent years, but need to observe longer period for the trend in future.

1.3 Disease burden of obesity

Obesity is getting more and more concern to the public and become an important issue in public health in terms of the global upward trend in prevalence and incidence, and also the huge economic burden of morbidity and mortality to the medical sector, community and individual family. Studies revealed that obese people may have higher risk of non-communicable diseases (NCD) including type 2 diabetes, high blood pressure, heart disease, stroke, high blood cholesterol and cancers such as colorectal cancer and breast cancer[1,3]. Cardiovascular diseases, including mainly heart diseases and stroke, which were the leading cause of death in 2012[1,3].

1.4 Risk factors for obesity

Obesity is the outcome of energy imbalance, hence excessive energy stored in body leading obesity as a result[1,3]. Common risk factors for obesity are unhealthy dietary practice, for example excessive energy intake due to consumption of high calorie, high fat and low fiber food. Bes:



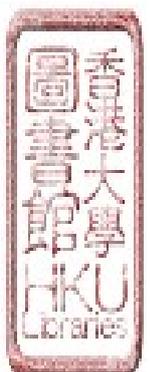
sedentary lifestyle of inadequate physical activities can cause accumulation of body fat as well. Moreover, aging is also one of the causes for obesity as the metabolic rate decrease with age[3]. Furthermore, environmental and societal elements are important factors, such as governmental policy, education, health facilities, urban planning, choices and accessibility of healthy food, etc[1]. An environment and society not supporting healthy eating and more physical workout may prone to risk of obesity of the population[1].

1.5 Treatments for obesity

Obesity and its related NCD are preventable[1]. Supportive environments and communities are important factors to provide healthier affordable food to people and available facilities to enhance people to have more physical workout in combating obesity[1].

In individual basis, people should live a healthy lifestyle to reduce risk of obesity[1, 3]. This could be achieved by limiting energy intake by adopting healthy dietary practice to have a balanced diet with food in the right amounts, and increasing fibers intake, and also having regular physical workout as a daily routine[1, 3]. Prevention is better than cure. To reduce weight, to reduce risk of getting chronic NCD[6]. Long term weight management and maintaining good health are the goals, and can be achieved by practicing healthy lifestyle, healthy eating habit and more physical activities[6].

Apart from lifestyle modification, approved drug treatments including short term treatment, long term treatment and combination drug treatment are available to reduce weight[7]. The drug treatments are effective in some patients resulting in weight loss ranging >30% to around 70% outcome according to some studies, but there are various side effects than placebo, more cardiovascular and metabolic risk, which may lead to possible cardiovascular problems and mortality[7].



Besides, surgical treatment namely bariatric surgery is also one of the options for some obese patient who had failed lifestyle intervention and drug treatment for weight reduction[8]. Bariatric surgery enhances better weight loss and subsequent maintenance in these patients, but requires comprehensive effort from expertise in different aspects including surgeon, physicians, dieticians, counselors and also hospital support, etc[8].

1.6 Cryolipolysis for obesity treatment

Apart from the mainstay of aforesaid weight management (i.e. healthy dietary practice and regular physical workout, drug treatment and surgical intervention), cosmetic procedures are getting more and more popular in community to serve this purpose. Liposuction remained a popular procedure for body contouring but invasive, we noted news about death as complication after received liposuction procedures from time to time, some news found in local newspapers are attached in figure 1.

Figure 1: News about death as complication after received liposuction procedures



Cryolipolysis is a new and noninvasive technique in cosmetic procedure, which is claimed to be effective even in single treatment and safe, to reduce fat in localized region[9,10,11]. The marketing strategies and promotion of cryolipolysis are extensive in Hong Kong, some examples are attached in figure 2. We can see the advertisements in almost every channel of mass media. It claimed that single treatment could reduce more than 20% of fat at treated site, but the adverse effects were



mentioned in the advertisements. It was also a hot topic in many public discussion forum.

Figure 2: Advertisements of cryolipolysis in Hong Kong



Cryolipolysis (Devices including CoolSculpting® ; ZELTIQ Aesthetics, Inc., Pleasanton, CA, USA) was approved by US Food and Drug Administration (FDA) for non-invasive body contouring intervention to flank and abdominal fat in August 2010 and to fat in thighs in April 2014[9]. The underlying mechanism is cooling induced apoptosis of adipocytes without affecting other cells and subsequent inflammation response leading to later digestion by macrophages, this is because the adipocytes are more susceptible to the cold stimuli hence the fat cells undergo apoptosis while other skin cells remained intact[9]. The fat volume in the treated area will reduce after few weeks post-treatment, while septa of connective tissues are thickened as revealed by histology examination. The device is a cooling machine applicable to fat bulging area with a cup shape applicator applied to the tissue concerned (treatment region of body part) via vacuum sucking mechanism. The treatment region was cooled for around 45 minutes each time. The consumer can go home and perform daily function right after the treatment. Regarding the treatment cycle regime, usually 1 treatment is enough for flank region, while the back and thighs usually require 2 treatment sessions receive around 8 week-interval to have better result for fat reduction. The procedure may cause pain during treatment, and also post-treatment transient numbness and bruises for up to a week [9-11].



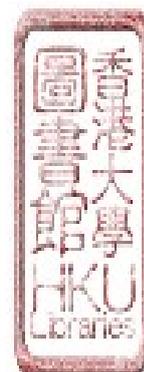
1.7 Aims and objective

From the above literature search information about obesity and the epidemiological findings, obesity is an important issue in public health that we should address.

Cosmetic procedures become more and more common in beauty industry and arouse interest of the population to have a trial. Liposuction remained a popular invasive procedure for body contouring. However, repeated news report about death as complication after received liposuction procedures were noted in recent years. In this regards, the growing popularity of cosmetic interventions poses safety concern to the community.

Cryolipolysis is a new advance in cosmetic procedure, claimed to be noninvasive and effective, which is hot in the beauty market in recent years, seems giving people safer alternatives and better choice of fat reduction in terms of cosmetic procedures.

The aims and objective of this systemic review is to review the effectiveness and adverse effect of cryolipolysis in fat reduction from all the relevant articles identified in available database up to May 2015.



Chapter 2 – Methods

2.1 Search strategy

The systemic literature search was conducted by using PubMed, Medline, and Google Scholar to identify the appropriate Journals and papers in English that discuss about the topics up to May 2015. Further articles were located by using Google and Yahoo search. The key words including “cryolipolysis”, “coolsculpting”, “noninvasive fat reduction”, “body contouring”, “new advance in fat reduction” were applied in the searching process. The reference lists of the articles identified during searching were also reviewed and those relevant articles were selected as well.

2.2 Inclusion criteria

Relevant journals and articles in English containing empirical data were selected despite study design. Full text papers were included for detail evaluation. A search filter was applied to limit the articles to full text in English in the PubMed.

2.3 Exclusion criteria

Articles not in English were excluded. Besides, editorials, letters or articles from unknown sources were excluded also. Duplicated and irrelevant articles were deleted. Besides, all advertisements, beauty centers webpages, personal blogs and articles of unknown author found in public discussion forum were excluded.

2.4 Outcome measures

To achieve the aim of the study, literatures selected were compared based on the following d

- i. Study design including the number of patients recruited in the treatment and control groups.
- ii. Patient demographics such as age, gender, BMI, ethnicity, method and tested sites, fo



up period

- iii. Assessment of effectiveness, that is the outcome measures, laboratory/histology findings, patients satisfaction, investigator assessment
- iv. Assessment of adverse effects such as the reporting of common side effects and rare complication

Further elaboration regarding the assessment of effectiveness, fat thickness was measured by ultrasound (USG) or histology examination (HE) or pinch test examination. While the circumference of some body part such as thigh was measured by caliper measurement. In some study, the fat amount or volume was measured by computer tomography (CT) and three dimensional photography (3DP). The visible appearance was recorded by clinical photography. One study used 5-point scale questionnaires (5psQ) for evaluation of the improvement after treatment.

For the assessment of the adverse effect, patient reporting of discomfort and physical complaint were recorded, some study examined the nerve damage and structural change by HE. Besides, blood tests on lipid profile were studied in some studies. Quatitative sensory testing (QST) was used in some study to assess the change in sensation, including the mechanical and thermal pain thresholds, after the cryolipolysis procedure.

Regarding assessment of the studies quality, the Quality Assessment Tool for Quantitative Studies of Effective Public Health Practice Project was applied to evaluate the quality grade based on a three-grade rating (1= Strong, 2 = Moderate, 3 = Weak) to all studies selected. The questionn: and the dictionary were used for the evaluation[12-14].

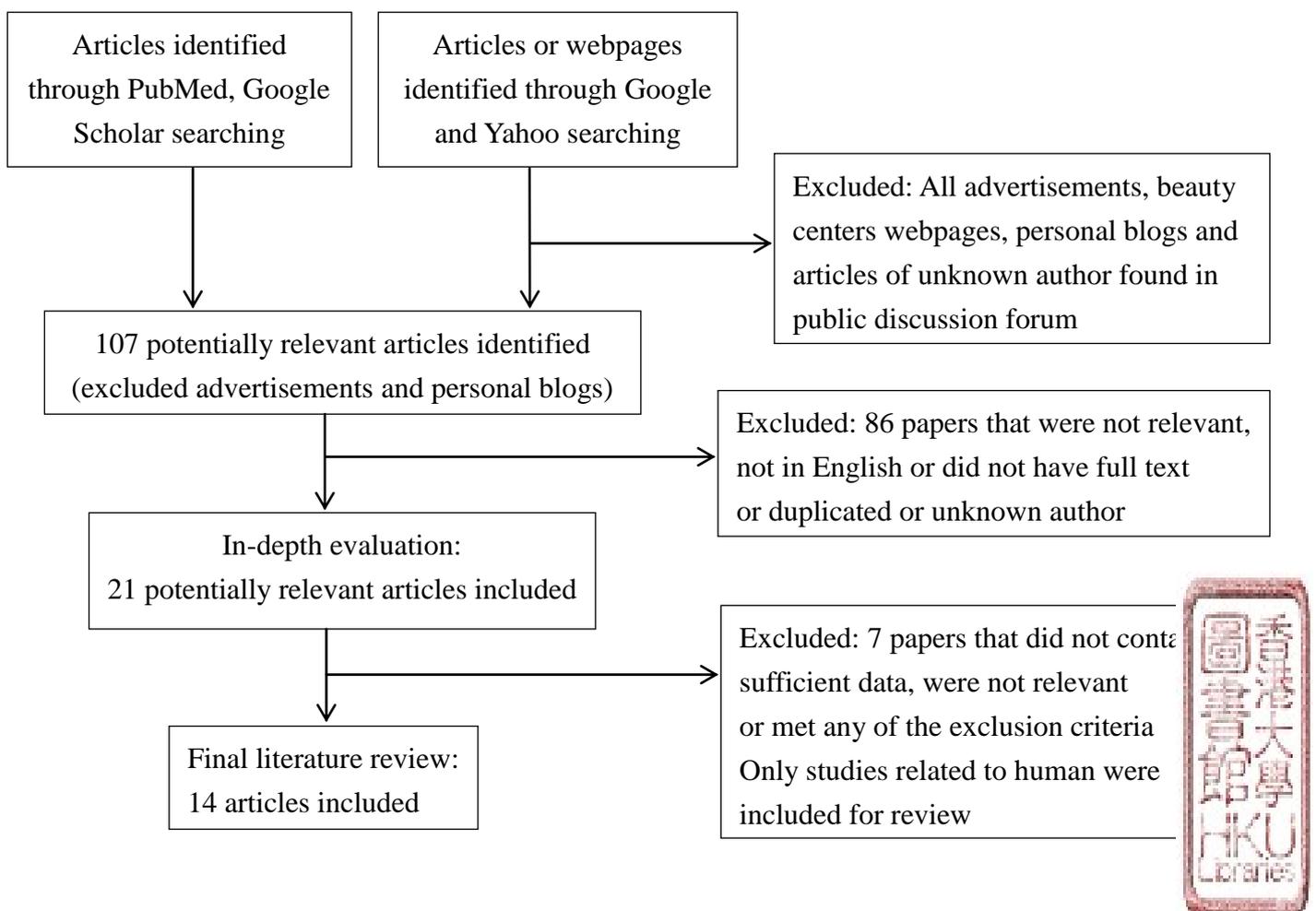


Chapter 3 – Results

3.1 Selection of studies

A first search was performed by using the key words (cryolipolysis, coolsculpting, noninvasive fat reduction, body contouring, new advance in fat reduction) generated articles. Among these, 86 articles were excluded after review of the titles, language, abstracts and availability of full text. Some were excluded as damaged link and hence failed to access the articles online. Besides, further 7 articles were excluded as they were not specific and relevant to the study topic or did not contain original empirical data. At the end, 14 were selected in the literature review. The literature searching process is illustrated in Figure 3 below.

Figure 3 – Process of literature search



3.2 Summary of studies

The 14 articles included 12 case-control study and 2 retrospective study reports related to human subjects[17-30]. All the articles identified were relevant to the study topic.

3.3 Effectiveness and adverse effect of cryolipolysis in fat reduction

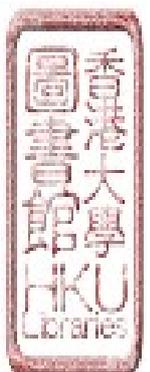
Before clinical trials were performed in human subjects, some tests were carried out in animal subjects to evaluate the effectiveness and adverse effects of cryolipolysis [15-16].

The two trials in pigs model were conducted in 2008 and 2009, 4 pigs were recruited in each study [15-16]. Both study showed more than 30% to 53% reduction in fat layer by USG and HE in treatment sites after received controlled local skin cooling, i.e. the cryolipolysis procedure[15-16]. One study revealed that fat cells were most susceptible to lower temperature and longer duration of treatment, showing more fat damage ($P < 0.001$)[12]. Regarding the adverse effects, one study reported mild skin necrosis and pigment change after treatments were noted in some treatment areas in pig, but no scarring or ulcerations were observed[15], while the other study did not report any adverse effects[16].

A summary of the case control studies on effectiveness and side effects of cryolipolysis in animals is illustrated in Table 3 for details.

Afterwards, many trials were conducted in human models and showed positive results[17-28].

Regarding a controlled trial performed in 2009[17], 10 human subjects were recruited to receive single treatment of controlled cooling treatment to test sites with the untreated side as control. The outcome was assessed by USG and HE. The average fat loss was found to be around 20% and

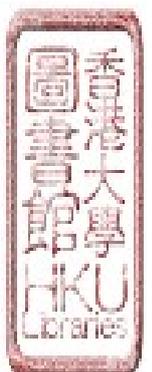


at 2 and 6 month time interval post-treatment respectively. Regarding the adverse effects, it was assessed by clinical examination of sensation study and patient self-reporting. Transient decrease in sensory feeling was reported, but no long term change in sensation was reported, and no skin problem or nerve damage was found[17]. Another study published in 2009 recruited 42 human subjects for receiving controlled local skin cooling, around 80% showed clinical improvement 2 to 4 months after received the treatment[18].

In 2012, two trials on human subjects by applying different models of cryolipolysis to reduce fat were published[19-20]. One trial recruited 33 human subjects, half of them received one treatment and the rest received two treatments in test sites, untreated side as control[19]. The outcome was measured by USG and showed around 14% and 7% significant mean reduction in first and second treatment respectively[19]. While the other study also showed significant decrease in fat thickness and also mean circumference by 3cm and 4.5cm respectively by using pinch test [20]. Regarding the adverse effects, one study reported transient redness, numbness and bruising, but no report of long lasting sensory alternations[19]. And the other study reported erythema, slightly increase in cholesterol and triglyceride level but within normal range[20].

A controlled trial was performed in 24 human subjects in 2013 showed similar findings, the average fat loss was around 20% by CT examination. Transient adverse effects such as swelling, pain, and numbness were reported[21].

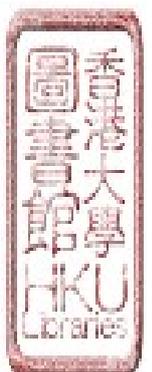
Five controlled trials published in 2014 were identified with 11-20 human subjects were recruited subjects and untreated side as control site[22-25]. One study assessed the outcome by both human subjects and dermatologists by using 5psQ, the average point of assessment by the human subjects was good to excellent improvement[22]. While the average point of assessment by dermatologists was moderately satisfactory results. Both assessments were significant by the P-v



Transient adverse effects including erythema, bruising and reduction in sensation were reported[22]. Another controlled trial assessed the outcome by a 3DP and caliper measurement[23]. There was reported around 40cc loss in fat volume at 2 month post-treatment in comparing the test and control sites. Besides, there was also reported a mean decrease of 7mm in caliper at 2 month post-treatment in comparing the test and control sites. Both results were significant by the P-values. Nil adverse effects were reported in the study[23]. Another two studies measured the outcome by clinical photos and USG for assessment[24-25]. One of the two controlled trial assessed the outcome by USG and clinical photos[24], revealing that the mean fat loss was around 20% or 3.3mm decrease in fat layer thickness, the result was significant as 95% confidence interval not covered 0. And there was visible fat reduction in inner thigh contour by the clinical photo assessments. Transient adverse effects such as numbness and pain were reported in the study[24]. The other study showed that the mean fat loss was around 13%, and nil adverse effects were reported[25]. One study assessed the outcome by clinical photos and noted an average around 40% improvement with evaluation by 4 blinded physician[26].

In 2015, two more studies were published[27-28]. One study assessed the outcome by clinical photos and circumference[27]. The result showed significant decrease in circumference by 0.41 and 0.72cm at 3 and 6 month interval visit respectively. Transient pain, redness and dysesthesia were reported as adverse effect in the study. Overall more than 60% of patients were satisfied with the outcome during follow-up visits[27]. The other study studied the pain effect due to cryolipolysis and assessed the outcome by QST and skin biopsy[28]. The result showed that the cryolipolysis procedure induced an obvious reduction in mechanical and thermal pain sensitivity, and might persist beyond one month time[28].

A summary of the case control studies on effectiveness and side effects of cryolipolysis in humans is illustrated in Table 4.



Apart from trials discussed before, two retrospective studies performed in 2013 were identified[29-30].

One study collected data from 528 patients who had cryolipolysis performed in the past two years[29]. The data collected were mainly about the frequency of treatment and related complications after the procedure. Nil data was reported on effectiveness in the study. Transient pain or neuralgia was reported as main side effect[29]. The other study collected data from 518 patients who had cryolipolysis performed in the past three years[28]. The data collected were mainly the outcome, side effect of the treatment with assessment by patient surveys and pain score, caliper measurement and clinical photos. The mean caliper reduction in fat layer was 23% at 3 month post-treatment, and no adverse effects were reported. And more than 80% of patients showed improvement in investigator assessment. Only transient pain or neuralgia were reported in 3 patients and no major side effects were reported in the study[27].

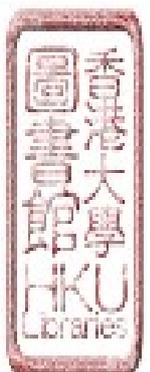
A summary of the retrospective studies on effectiveness and side effects of cryolipolysis is illustrated in Table 5.

3.4 Assessment of study quality and resultant impact on validity of evidence

Study quality refers to the study design, method and execution. The outcome should be assessed by appropriate tools.

The Quality Assessment Tool for Quantitative Studies of Effective Public Health Practice Practice was applied to evaluate the quality grade based on a three-grade rating (1= Strong, 2 = Moderate Weak) to all studies selected[12]. The questionnaires and the dictionary were used for the evalua

This tool was developed for the application in public health and could be applied to pa



discussing various topics in Public Health aspect. The tool was tested on the content and initial construct validity and inter-rater reliability and found to have strong methodological rating. The questionnaires consists of many components for rating including selection bias, study design, confounders, binding, data collection method, withdrawals and drop-outs, intervention integrity and analyses[13]. While the dictionary gives you a guide how to answer the questionnaires and delineate the grading[14].

The overall grade for the studies selected should be grade 3 (weak) as all the controlled trials selected were not randomized, the level of evidence and studies quality would be weakened. Moreover, the studies selected patients from a source the clinic, which may poses selection bias. Both patients and investigators were not blinded in the studies and the no details about confounders were elaborated.

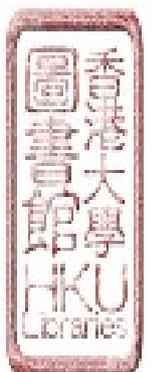


Table 3 – Summary of case control studies on effectiveness/side effects of cryolipolysis in animals

Author, Year	Study Design	Sample Size	Interventions	Control	Outcome Measures	Post-treatment Findings	Adverse Effects Reported
Dieter Manstein [15], 2008	Controlled trial 3.5months	4 Pigs	Controlled local skin cooling in 11 sites (including flank, abdomen and buttock) by Zeltiq	Yes, untreated side	-USG -HE	USG: ~ 40% total fat loss in buttock test site. Fat damage was greater at lower temperatures (F=16.11, P<0.001) and increased over time (F=32.77, P<0.001) HE: Loss of adipocytes, the appearance of lipid-laden mononuclear inflammatory cells, and local thickening of fibrous septae were noted	Superficial epidermal necrosis was noted in some of the treated sites, with post-treatment hypopigmentation noted, but no scarring or ulcerations reported
Brian Zelickson [16], 2009	Trial 3 months	4 Pigs	Controlled local skin cooling by Zeltiq	Yes, untreated side	-USG -Photography -HE	USG: Fat reduction in the superficial fat layer of 33% HE: 50-53% decrease in superficial fat thickness	Nil

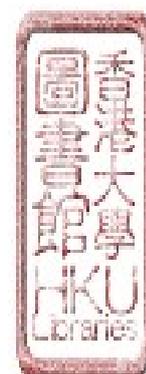


Table 4 – Summary of case control studies on effectiveness/side effects of cryolipolysis in human

Author, Year	Study Design	Sample Size	Interventions	Control	Outcome Measures	Post-treatment Findings	Adverse Effects Reported
Sydney R. Coleman [17], 2009	Controlled trial 6 months	10	Controlled local skin cooling by Zeltiq	Yes, untreated side	- USG - Clinical exam (Sensation study) - HE	Normalized fat layer reduction of 20.4% at 2 months and 25.5% at 6 months after treatment	Transient reduction in sensation, no report about lasting sensory alterations, skin/nerve damage
Rosales-Berber IA[18], 2009		42	Controlled local skin cooling by Zeltiq			79% of the subjects reported a clinical improvement within the first 2-4 months following the treatment	
Samantha Y. Shek[19], 2012	Controlled trial 6 months	33 Chinese	Controlled local skin cooling by Zeltiq - Gp A: 1 Rx - Gp B: 2 Rx	Yes, untreated side	- USG - Questionnaires	Group A: Mean reduction was 14.67%, median of 15.1 and standard deviation of 9.9. Group B: Mean reduction after the first and second treatment was 14.0% and 7.2% respectively, (P = 0.012) by the Mann–Whitney test	Transient redness, bruising and numbness reported. No long term alternation in sensory function was reported.
G. A. Ferraro[20], 2012	Controlled Trial 12 months	50	Controlled local skin cooling by Ice-Shock Lipolysis	Yes, untreated side	- Circumference - Pinch test (Fat thickness) - Photography - Questionnaires	The mean reduction in fat thickness after treatments was 3.02 cm. Circumference was reduced by a mean of 4.45 cm. (P<0.05).	Transient erythema Mildly elevated cholesterol and triglyceride reported, but within normal limit
Kyu Rae Lee[21], 2013	Controlled trial 3 months	14	Controlled local skin cooling by Zeltiq	Yes, untreated side	- Circumference - CT (Femoral fat amount)	CT: The fat reducing efficacy of cryolipolysis was -19.55%.	Transient numbness, pain and swelling reported
Jiehoon Kim[22], 2014	Controlled trial 3 months	15	Controlled local skin cooling by Micool™	Yes, untreated side	- 5psQ by patients and dermatologists, by SPSS analysis	5psQ by patient: Mean score was 1.7, good to excellent improvement or 50% to 100% subcutaneous fat reduction. 5psQ by dermatologists: Mean score was 2.1, moderately satisfactory results. (P<0.05)	Trans: bruise decre: sensat



Lilit Garibyan[23], 2014	Controlled trial 2 months	11	Controlled local skin cooling by Zeltiq	Yes, untreated side	- 3DP (Fat volume) - Caliper measurement	3DP: A mean absolute difference of 39.6 cc at 2 months (P<0.001). Caliper: A mean reduction of 7 mm at 2 months (P<0.001).	Nil
Gerald E. Boey[24], 2014	Controlled trial 4 months	11	Controlled local skin cooling by Zeltiq	Yes, untreated side	- Photography (Visible fat reduction) - USG	USG: 83% of subjects attained some level of fat layer reduction. Normalized mean reduction in fat layer thickness was 20% (no 95% confidence interval overlap with 0). Photography: visible fat reduction in inner thigh	Transient numbness and tenderness reported
Gerald E. Boey[25], 2014	Controlled trial 4 months	17	Controlled local skin cooling by Zeltiq ± post treatment massage	Yes, untreated side	- Photography (Visible fat reduction) - USG	USG: The normalized mean fat layer reduction was 12.6% (mean 2.6mm) for the non-massaged side and 21.0% (mean 4.2mm) for the massaged side.	Nil
Eric F. Bernstein[26], 2014	Controlled trial 3 months	10	Controlled local skin cooling by Zeltiq, new applicator for flank fat	Yes, pre-treatment assessment as baseline	- Photography (Visible fat reduction)	A high degree of improvement was reported by 4 blinded, physician evaluation of standardized photographs before and after treatment. Improvement was scored from 0(none) to 10 (complete) and showed an average 4.3 point (43%) improvement.	Transient erythema, edema, bruising, and numbness or tingling reported
Rungsima Wanitphak deedecha[27], 2015	Controlled trial 6 months	20	Controlled local skin cooling by Zeltiq, new applicator for arm and thigh fat	Yes, pre-treatment assessment as baseline	- Photography (Visible fat reduction) - Circumference measurement	Significant circumference reduction of 0.41 and 0.72 cm at 3 and 6-month follow-up visits (p=0.017), respectively. In this present study, 76.5 and 64.7 % of patients were satisfied with the results at 3- and 6-month follow-up, respectively.	Transient pain, erythema, dysesthesia, purpura



Lilit Garibyan[28], 2015	Controlled trial 2 months	11	Controlled local skin cooling by Zeltiq	Yes, untreated side	<ul style="list-style-type: none"> - Quatitative sensory testing (QST) - Skin biopsies 	<p>Cryolipolysis produced a marked decrease in mechanical and thermal pain sensitivity.</p> <p>Hyposensitivity started between 2-7 days after cryolipolysis and persisted for at least 35days post-treatment. Skin biopsies revealed that cryolipolysis decreased epidermal nerve fiber density as well as dermal myelinated nerve fiber density, which persisted throughout the study.</p> <p>This study suggested that controlled skin cooling to specifically target cutaneous nerve fibers has the potential to be useful for prolonged relief of cutaneous pain and might have a use as a research tool to isolate and study cutaneous itch-sensing nerves in human skin.</p>
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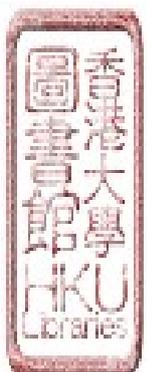
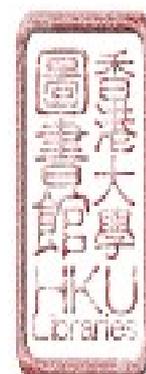


Table 5 – Summary of retrospective studies on effectiveness/side effects of cryolipolysis

Author, Year	Study Design	Sample Size	Outcome Measure	Post-treatment Findings	Adverse Effects Reported
W. Grant Stevens [29], May 2013	A retrospective chart review	528 patients with cryolipolysis done from Jan 2010 to Dec 2012	Assess at post-Rx 2 or 3 month Data collection and outcome measure on <ul style="list-style-type: none"> - The number of patients treated - The total number of treatment cycles - The average number of treatment cycles per patient, treatment areas, and procedural complications 	Nil data on effectiveness	Transient pain/neuralgia were reported
Christine C. Dierickx [30], 2013	A retrospective study	518 patients Study was conducted from Jul 2009 to Feb 2012	Assess at post-Rx 1 month, 3 month Data collection and outcome measure on <ul style="list-style-type: none"> - Safety: reports of side effects. - Tolerance: reports of pain scores and patient perception of treatment duration - Clinical outcomes: patient surveys, caliper measurements, and assessment of photographs 	Caliper measurements demonstrated 23% reduction in fat layer thickness at 3 months. Abdomen, back, and flank treatment sites were most effective, with 86% of subjects showing improvement per investigator assessment	Nil.



Chapter 4 – Discussion

4.1 General effectiveness of cryolipolysis

All trials [17-28] and the two retrospective studies [29-30] showed promising effects in fat reduction after cryolipolysis. All trials on human models showed [17-28] 13% to 23% reduction in fat thickness after single treatment.

All trials used untreated side or pre-treatment baseline data as control. Regarding the machine models, one study applied controlled local skin cooling by Micool™ and one by Ice-Shock Lipolysis, the rest studies applied Zeltiq. Regarding the tested areas, the studies selected one or more body parts namely flank, abdomen and thigh as treatment area. For assessment of outcome, these studies applied various assessment methods such as questionnaires, clinical photos, caliper measurement, USG, CT scan, 3DP and skin biopsies test to measure the effectiveness of cryolipolysis in fat reduction which may affect the interpretation of results and difficult for comparison. A standardized assessment method should be applied to enhance comparison of the effect and outcome of the cryolipolysis procedure relating to machine model and treatment site. There was no sufficient information so far to provide that which body parts are most responsive to the procedure.

Majority of trials applied one single treatment of cryolipolysis to tested area, but some studies [19] applied two treatment and showed significant fat reduction after each treatment with greater extent after the first treatment. Hence, multiple treatment might still show to be effective in fat reduction but in a lesser extent. Another study [25] assessed the effect of post-treatment massage as we showed better result of fat reduction in massaged side. Nevertheless, further studies are required to assess the effectiveness of multiple treatment and post-treatment massage in fat reduction.



Moreover, there are many factors affecting the effectiveness of cryolipolysis in fat reduction including patient factors and treatment factors. But there is no detail description in the studies about the selection criteria of patients recruited or standardized treatment settings, hence it might pose bias or error in assessing the outcome and results. Therefore, patient selection criteria and standardized treatment protocol should be well delineated in future studies.

4.2 Adverse effects of cryolipolysis

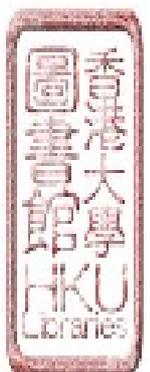
A low profile of side effects of cryolipolysis is the selling point and promotion strategy in the beauty market. Among the studies, transient symptoms including erythema, swelling, pain, numbness and bruising as the adverse effects were reported, and no report of sensory or skin problem or nerve damage were received [17-30]. The side effects were reported by patients or assessed by sensation study, QST and skin biopsies test in the studies. These side effects resolved spontaneously without treatment usually within a month as reported in the studies.

From literature search, some case reports[31-32] stated that paradoxical adipose hyperplasia (PAH), an infrequent side effect with incident rate of around 0.005%, was reported in some cases after cryolipolysis procedure. The condition seems persisting and is not resolved spontaneously. But there was no risk factor could be identified, it was observed to be more common in men. Further information was required in future study to provide details about PAH.

4.3 Limitations of study

Only English articles were included, which may limit the number of publications available for review. Moreover, the author was the only one reviewer in data extraction to select articles for review, may lead to bias in literatures selection and overlook of mis-matches.

Although all trials and retrospective studies showed promising effects[17-30], the sample size

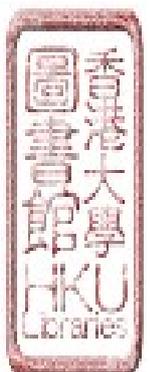


small, trails were not randomized in subject selection and no long term follow-up of the outcome was conducted, hence this may limit the quality of the information could be obtained from the studies, and there might be recall bias in the two retrospective studies which had collected data from more than 500 patients[29-30].

Furthermore, no study was conducted in Hong Kong, since many data available were from Caucasians, the generalizability to be applied in Hong Kong population is questionable.

From business point of view, cryolipolysis is a new advance in cosmetic industry, which could bring the industry extra profit, hence possible hidden commercial interests might occur and could affect the outcome and quality of trials.

A further large scale case control study should be performed to confirm the effectiveness and adverse effect of cryolipolysis in fat reduction in long term. Long follow up duration and larger sample size should be proposed to observe the sustainability of the effect of body contouring and fat reduction as well as the adverse effects or complications in long run. Moreover, the effectiveness and adverse effects of different machine models of cryolipolysis may be explored in future study. Furthermore, the role of cryolipolysis in pain control could be further studied as well[28]. Regarding the commercial interest concern, the studies should be proposed to be conducted by government or academic authorities if possible to avoid potential conflict of interest.



Chapter 5 – Conclusions

The increasing popularity of the cosmetic procedure nowadays poses public concern on the effectiveness and safety of the procedures. Regarding new advance, cryolipolysis is promoted as a new and noninvasive technique, claimed to reduce 22% fat after single treatment and safe.

This project reviewed 14 articles about the effectiveness and adverse effect of the noninvasive procedure cryolipolysis in fat reduction. All 12 trials[17-28] and 2 retrospective studies[29-30] showed promising effects in fat reduction after cryolipolysis with transient adverse effects reported only[17-30]. Hence, cryolipolysis is effective and safe in fat reduction. However, the sample size in all trials was small without long term follow-up of the outcome[17-30], and there might be recall bias in the two retrospective studies which had collected data from more than 500 patients[29-30].

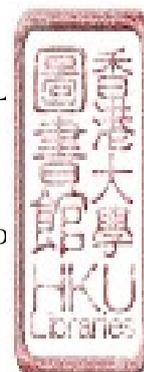
The demand for people to pursue good body contour in cosmetic industry persists, hence there is a need to provide safe and effective way for fat reduction in this aspect. Accurate and updated information should be conveyed to customer for their consideration before purchase of the cryolipolysis package. A further large scale case control study should be performed to explore more on the effectiveness and adverse effect of cryolipolysis in fat reduction in different body parts or different machine models. Moreover, longer follow up study should be considered to evaluate the sustainability of fat reduction effect and long term adverse effect in future studies.

In conclusion, although balanced healthy lifestyle such as healthy eating and more exercise should remain the mainstream of management in combating obesity, and should be promoted and emphasized in public health education[1, 3], available studies showed that cryolipolysis is effective and safe for fat reduction, but there should be detailed research to help formulating standard protocol of the procedure to safeguard the safety of customers.

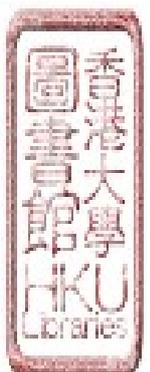


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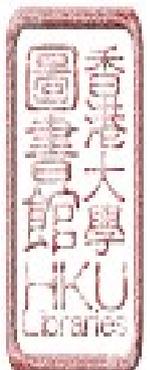
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