Non-Invasive Cryolipolysis for Body Contouring in Chinese—A First Commercial Experience

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Background: The objective of the study is to determine the clinical efficacy and patient satisfaction of a novel cryolipolysis device (Zeltiq®) for body contouring in Chinese after a single treatment and after 2 treatments at a commercial setting.
Materials and Methods: Two groups of patients were recruited for this procedure at their own cost. Group A, 21 subjects, received a single treatment and group B, 12 subjects, received 2 treatments, average 3 months apart using the Zeltiq Breeze System®. The thickness of fat at the treatment site was measured by a caliper and the data were collected at baseline and 2 months post-treatment. Standardized clinical photos were also taken at baseline and follow-up visits. Subjective assessment was carried out in the form of a questionnaire. Any adverse effects were documented. Statistical analyses were performed on the data to compare the efficacy after a single treatment and after 2 treatments.
Results: The first group of subjects, received a single treatment, showed that there was a significant improvement ($P < 0.0001$). The second group of subjects showed that the improvement was significant after 1 and 2 treatments when compared to the baseline. The extent of improvement after the second treatment however, was not as dramatic as the first treatment.
Conclusion: Non-invasive cryolipolysis is effective for body contouring in Chinese. It is shown to have a further improvement with subsequent treatment sessions but of a lesser extent. The second treatment was statistically significant for abdomen, though not for love handles. Lasers Surg. Med. 44:125–130, 2012.

Key words: cryolipolysis; fat reduction; non-invasive body contouring; multiple treatments

INTRODUCTION

Body shape and image are negatively impacted by unwanted local subcutaneous fat. Fat removal and body reshaping are increasingly popular cosmetic procedures. Liposuction is still the most effective treatment for the removal of local subcutaneous fat. However, it is an invasive procedure with surgical risks, such as infection, scarring, hematoma, and deep vein thrombosis/pulmonary embolism as well as specific risks associated with general anesthesia [1][2]. The most common complications of liposuction are contour irregularities and transient bruising [3]. In sight of these risks and the downtime, various cosmetic procedures and devices have been developed to remove or reduce unwanted local subcutaneous fat non-invasively with minimal downtime. Focused ultrasound generates primarily mechanical effect and in doing so, ruptures the adipocyte membrane with minimal damage to neighboring blood vessels, nerves, and connective tissue. Whilst some reported positive results [4,5], a study based on Chinese subjects found that the improvement was not significant [6]. Combination radiofrequency, infrared light, and mechanical tissue manipulation devices are found to be effective in restoring the fat distribution and releasing the fibrous septae thus reducing the appearance of cellulite rather than removing fat [7]. Another device that uses dual-wavelength laser (650 and 915 nm) suction and massage device can be used for the treatment of cellulite [8]. It can also be used to decrease body circumference but its efficacy has yet to be evaluated.

The technique of applying cold to the skin was looked into based on some studies that have suggested that fat cells may be more sensitive to cold than other tissues [9–11]. Initial animal studies showed that cryolipolysis induced by controlled exposure to cold can induce selective damage to the subcutaneous fatty tissue, resulting in reductions in the superficial fat layer of pigs [12,13]. The serum lipid level of the pigs was normal over the 3-month period following treatment. Two recent published abstracts reported a reduction of fat layer after a single treatment [14,15]. The purpose of the study is to analyze the efficacy of non-invasive cryolipolysis in Chinese. The other objective is to look at the effectiveness after multiple treatments.

MATERIALS AND METHODS

Two groups of subjects were analyzed in this study. All treatments were performed at the subjects' own cost at a

Conflict of interest: None declared.
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commercial setting. Group A belongs to a prospective study where subjects above 18 years of age with visible fat bulge on the abdomen or flanks (love handles) requesting treatment at their own cost were screened. Those that met all inclusion/exclusion criteria were recruited into the study with written informed consent.

Subjects should not have undergone liposuction, other surgical procedures or any body contouring treatments in the area in the past 6 months. They were excluded if they have a history of cryoglobulinemia, paroxysmal cold haemoglobinuria, cold urticaria, areas of impaired peripheral circulation, Raynauds disease, pregnancy, scar tissue, or extensive skin conditions, such as eczema or dermatitis at the area, impaired skin sensation, open or infected wounds, and area of recent bleeding or haemorrhage. Subjects with obvious skin laxity or enrolled for other clinical studies were also excluded.

Potential side effects were stated on the informed consent form. They include stiffness of treatment area normally disappearing within 10 min, mild redness lasting for a few minutes to a few days, bruising which may last for several weeks, sensations, such as tingling, tenderness and/or soreness for 2 weeks, and temporary dulling of sensation for up to 8 weeks after the procedure.

The treatment sites were identified, assessed, and marked by the physician in charge. Prior to treatment, subjects' weight was recorded and the thickness of fat at the treatment sites was measured by a caliper. All caliper readings were taken by trained nurses. Each subject was measured and serviced by the same nurse at each visit. The measurement was carried out three times and the repeated value was recorded. The location of the site measured relative to the treatment area was recorded on a transparent plastic sheet. A control site was also measured by the same method. Clinical photos were taken by Canfield Monostand System® at fixed angles and posture, aiming to provide a relatively fair comparison pre- and post-treatment. The Monostand is a height adjustable, counter-balanced camera stage that allows the used to maintain a perpendicular aspect on the subject matter. Using a series of pre-determined markings on the floor, the user positions the Monostand at the pre-determined reference points to ensure that the reproduction ratio and focal distance are maintained throughout the image series. Using Mirror PhotoTools, the software uses a capture control module to trigger the camera. The camera parameters are set by the software and the camera captures the images into Mirror and the patient chart, along with the associated image data. The photographer positions the subject on a patient posing stage or mat, in front of a backdrop. The mat or stage is positioned using reference markings. The subject is rotated through a prescribed series of positions as indicated by the markings on the stage or positioning mat and images are acquired at each position.

Group A had one treatment, ranging from 2 to 4 treatment sites (i.e., 2–4 cycles per treatment), depending on the size of the area treated. Group B belongs to a retrospective study. We included patients who have had 2 non-invasive cryolipolysis treatments at the clinic, also ranging from 2 to 4 treatment sites. The first and second treatment sessions were on average 3 months apart. The CIF of the Zeltiq® non-invasive cooling device was pre-set at 41.6 (-73 mW/cm^2) and was applied for 60 min. The applicator used in this study is the standard size applicator. The study was completed before the availability of other applicator sizes.

Immediately after the cryolipolysis, subjects were asked to rate the comfort level (0 comfortable, 1 minimal discomfort, 2 tolerable discomfort, 3 painful, 4 intolerable) of the procedure and to describe the tissue texture as similar to adjacent untreated area, claylike or stiff. Any adverse effects were noted. The nurses followed-up on the subjects by phone, 1 day after the procedures. Subjects were followed up 2 months after the treatment. They were asked to recall if they experienced any redness, bruising, or numbness, and how long they took to subside. Measurement of fat thickness by caliper was taken at the same sites measured at baseline (test and control sites) with reference to the plastic sheet with previous markings made. Clinical photos were taken, using the same angles and posture with the Canfield Monostand System®. Any adverse effects were documented.

We compared the data collected at baseline and 2 months post-treatment from Group A by Wilcoxon signed Rank's test. We also compared the data from the treatment sites and the control sites and tested it with the Mann–Whitney test. Subjective assessment collected in the form of a questionnaire was tabulated into percentages for each category. Two non-blinded independent physicians assessed the treatment sites of the clinical photos taken and any improvement was recorded in a 4-point system (0 = no improvement, 1 = slight improvement, 2 = moderate improvement, 3 = good improvement, 4 = significant improvement).

For Group B, we also compared the data collected at baseline and 2 months after the first treatment, then prior the second treatment and 2 months after the second treatment to see if there was any further improvement. The Wilcoxon signed Rank's test was applied. The average percentage decrease was also looked at after the first treatment and after the second treatment. We also compared the data of the treatment sites with the control sites by the Mann–Whitney test. Two non-blinded independent physicians assessed the treatment sites of the clinical photos taken and any improvement was recorded in a 4-point system with a percentage as a general guideline (0 = no improvement, 1 = slight improvement, 2 = moderate improvement, 3 = good improvement, 4 = significant improvement).

RESULTS

Twenty-one subjects, 16 females and 5 males were enrolled into Group A, where a single treatment was provided at their own cost. The mean age was 46, with a range of 27–72. Their mean height was 1.6 m and the mean BMI was 23.96 at baseline. The mean BMI at the follow-up visit 2 months after treatment was 23.80, indicating

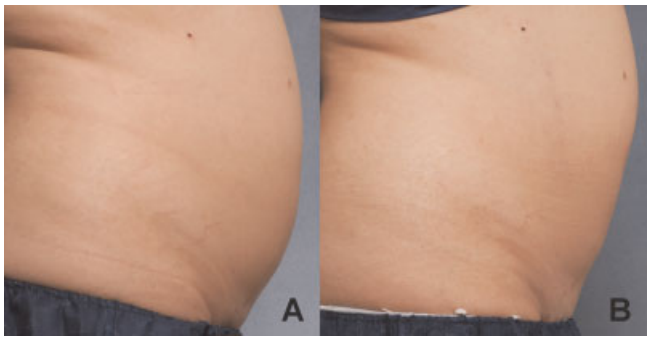

Fig. 1. Abdomen at baseline and 2 months after 1 treatment.

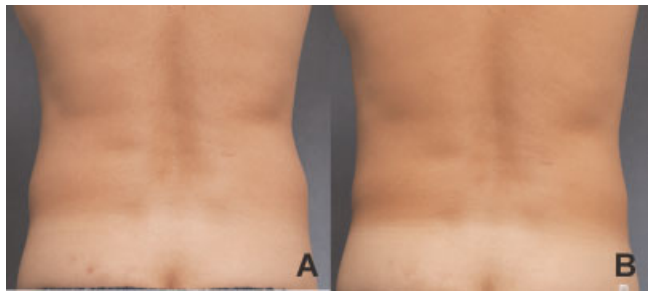

Fig. 2. Love handles at baseline and 2 months after 1 treatment.

that the weight of the subjects remained relatively constant throughout the study.

Each treatment site was exposed to CIP 41.6 (−73 mW/cm^2) for 60 min. Sixty-two percent of the subjects felt that the length of time required was just about right, whereas 38% thought it was too long. Eighty-one percent reported a noticeable difference in the area treated and on average, it took 4 weeks to notice the difference (range 2–7 weeks). Most subjects experienced improvement and their expectations were met. 76.1 of them fall in the category, noticeable to easily noticeable, with 71% experiencing a difference in the fit of their clothes. Fifty seven percent thought the treatment reached or exceeded their expectations, whereas 43% expected a more dramatic effect (Figs. 1 and 2).

The Wilcoxon signed Rank's test was applied to compare the baseline measurements and the 2 months post-treatment follow-up measurements taken by the caliper. A value of $P < 0.0001$ was generated therefore there is a statistically significant decrease in the thickness of fat after Zeltiq® treatment. The treatment sites and control sites were also compared to ensure that the decrease in fat thickness is due to the treatment itself. The pre- and post-treatment measurements of both sites were analyzed using the Mann–Whitney test. The degree of change pre- and post-treatment at the treatment sites were compared with the degree of change at baseline and follow-up at the control sites. $P = 0.001$ indicates there is a statistically significant difference between the changes observed at the treatment sites versus the control sites. The result is summarized in Table 1 and Figure 3. The average improvement based on caliper readings was 14.67% in this group of subjects, with a median of 15.1 and standard deviation of 9.9. This is calculated by taking the average of the percentage reduction (positive for reduction, negative for increase) in the fat thickness measured by the caliper. BMI was assessed as a covariate in one-way ANOVA to determine whether it had an effect on reduction in fat thickness and was not found to be a significant predictor ($P = 0.99$). Based on the clinical photos taken by the Canfield Visia System®, both physicians were satisfied with all the post-treatment results. Eighty-one percent of the subjects were rated to have moderate-to-good improvement. Subjectively, 80% felt satisfied to very satisfied, and the rest was indifferent. Eighty-six percent would consider having non-invasive cryolipolysis performed on another part of their body and the same percentage would consider recommending this treatment to family and friends.

In terms of adverse effects, 5 subjects (23.8%) reported redness after treatment and 2 subjects (9.5%) reported bruising, all of which resolved within 1 week. Six subjects (28.6%) experienced numbness which took up to 3 weeks to resolve. There was no permanent effect in sensory function.

A second group of subjects was recruited to investigate the efficacy of multiple non-invasive cryolipolysis treatments. Two treatment sessions, on average 3 months (mean: 88.1 days; SD: 44.8) apart were given. Total of 12 subjects were recruited, 9 females and 3 males. They were treated at the love handles and/or abdomen as requested at their own cost. Each treatment site was exposed to CIF 41.6 for 60 min. The mean age was 47 with a range of 35–60. Their body weight remained relatively constant, indicated by an average BMI of 22.5 at the beginning of the study and 22.3 at the end.

We looked at the data collected for the different treatment areas separately. For the abdominal area, we tested

TABLE 1. Summary of Group A's Result

	Caliper readings (cm)	Mean (SD)	Median	Range	*P*-value compare to baseline
Treatment site (N = 66)	Baseline	31.0 (6.23)	30.60	19.1–43.8	<0.001
	2 Month follow-up	26.5 (6.17)	26.68	12.3–43.8	
Control site (N = 45)	Baseline	23.5 (7.21)	23.00	11.7–40.3	<0.001
	2 Month follow-up	21.0 (6.07)	20.60	10.4–34.1	

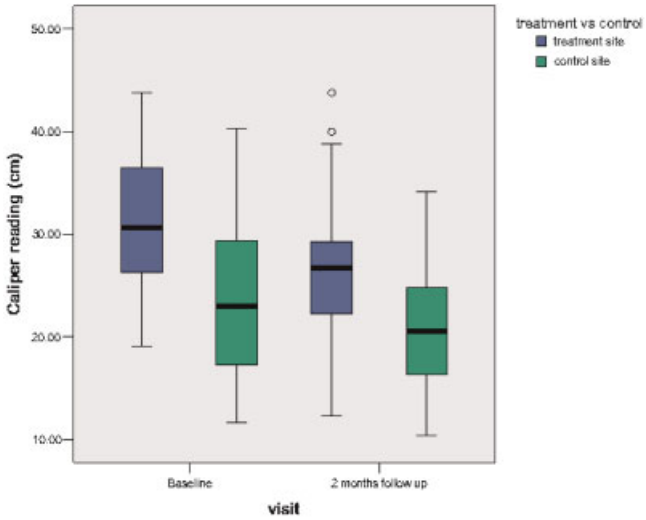

Fig. 3. Boxplot of caliper readings at treatment and control site (Group A).

the caliper readings measured at baseline and 2 months after the first treatment by the Wilcoxon signed Rank's test with a result of $P < 0.001$, Table 2a. Then the same test for the readings measured prior to the second treatment and 2 months after the second treatment was applied, generating a P-value of 0.020, Table 2a. The Mann–Whitney test, comparing the difference pre- and post-treatments at both sites, showed that there was a significant difference between the control and treatment sites ($P \leq 0.001$), whereas the control site remained unchanged, no significant difference statistically, pre- and post-treatments ($P = 0.199$). This indicates that, a second non-invasive cryolipolysis provided a statistically significant improvement in the fat thickness at the treatment site (Figs. 4 and 5). The average improvement after the first treatment was 14.0%, whereas the average improvement after the second treatment was 7.2%.

In terms of the love handles, we used the same statistical analysis for the data collected. The caliper readings measured at baseline and 2 months after the first treatment gave a P-value of 0.003 (Table 2b), and the readings collected prior to the second treatment compared to 2 months after the second treatment produced $P = 0.084$, no significant difference statistically (Table 2b). Again, we used the Mann–Whitney test which demonstrated a significant difference between the control and treatment sites ($P = 0.012$), and no significant difference at the control sites pre- and post-treatments ($P = 0.896$). The average improvement is calculated using the same method and there was a 13.4% improvement after the first treatment and a 4.3% improvement after the second treatment. The result is that there was some degree of decrease in fat thickness after the second non-invasive cryolipolysis at the love handles. However, it was not enough to be statistically significant. Group B's result is summarized in Figure 6.

DISCUSSION

Our study demonstrates that the use of non-invasive cryolipolysis is effective for diminishing localized subcutaneous fat. It has been shown histologically in previous human and animal studies that inflammation and adipose tissue loss were well correlated. There was maximum lobular panniculitis around 4 weeks after cold exposure, resolving about 3 months after. In the later phase, phagocytosis appeared to be accounted for the removal of adipocytes and loss of fat tissue [12].

A multicenter, prospective, non-randomized clinical study performed by Dover et al. [14] assessed 32 subjects with unilateral treatment on the flank or back. A contralateral untreated area was used as a control. Preliminary results based on ultrasound measurements taken from 10 subjects showed a fat layer reduction of 22.4% at 4 months post-treatment. Another study carried out by Riopelle et al. [15] assessed 10 male subjects with discrete fat bulges at the love handles. Five subjects had ultrasound measurement and an average of 18.2% reduction was found at 6 months after treatment. Comparing our findings, based on measurements taken with a caliper, a 14.7% reduction was found in Group A, 14.0% reduction at the abdomen in Group B, and 13.4% reduction at the love handles in Group B, were found 2 months after a single cryolipolysis treatment. Our values are slightly

TABLE 2a. Summary of Caliper Readings of Abdomen for Group B

	No. of treatment cycles	Mean	SD	P-value
Abdomen, treatment site (no. of subjects = 10)				
Caliper readings at baseline	23	27.0	7.8	<0.001
Caliper readings 2 months post-treatment	23	23.0	7.1	
Caliper readings pre-second treatment	23	23.3	8.2	0.020
Caliper readings 2 months post-second treatment	23	22.1	9.7	
Abdomen, control site (no. of subjects = 10)				
Caliper readings at baseline	18	21.1	8.5	0.010
Caliper readings 2 months post-treatment	18	19.2	7.6	
Caliper readings pre-second treatment	22	20.0	8.7	0.314
Caliper readings 2 months post-second treatment	22	20.4	9.2	

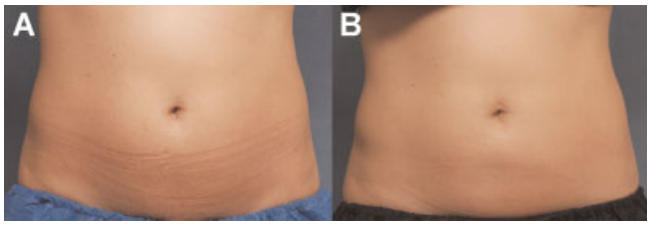

Fig. 4. Abdomen at baseline and 2 months after first treatment.

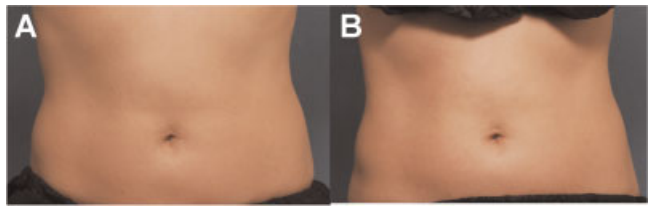

Fig. 5. Abdomen of the same subject pre-second treatment and 2 months after second treatment.

lower than those reported by the other 2 studies mentioned above. This may be because the measurements were taken at a later stage at those studies (3 months post-treatment vs. 2 months post-treatment), so more time was allowed for the inflammation and phagocytosis, thus the clearing of adipocytes to occur. Data collected along the same time frame is required for a fair comparison.

There is no published data on the effects of multiple treatments with the non-invasive cryolipolysis device. Our result demonstrates that a second treatment leads to a further improvement. In terms of the abdominal area, the improvement 2 months after the second treatment was 7.2% and was statistically significant. The improvement 2 months after the second treatment at the love handles was 4.3%, which was not enough to be statistically significant. All treatments were performed using the EZ APP 6.3. Both EZ APP 6.2 and 6.3 have identical cooling panel dimensions and treat the same amount of tissue. However, later in our clinical practice, we observed that the fit of the EA APP6.2 is better for our Asian patients especially at the love handles. This may contribute to the efficacy of the treatment, but yet to be proven. The smaller sample size (Table 2b) in the second treatment may also account for the statistics generated therefore a larger sample size would be preferred. A hypothesis is that the diminished effect in the second treatment may be because the thickness of fat at the original site has already decreased after the first treatment, so the anatomical area exposed to the second heat extraction is closer to the muscle layer. The vascular supply to the muscle layer may impede the efficiency of heat extraction so the fat closer to the muscle layer may not reach the optimal temperature of 4°C intended. There is also less total amount of fat is exposed to cold per treatment site in the second session. Another proposition is that adipocytes that survived the first treatment have a higher tolerance to cold. A study by Lee et al. [16] showed that adipose tissue cryopreserved at −20°C for 1 year is a reliable source of human adipose-derived stem cells and adipocytes. This indicates that some adipocytes stem cells are able to survive after exposure to low temperatures. We were unable to identify any common variable for the non-responders. Dr. Rox Anderson suggested that the difference in saturated and trans fats might "freeze" differently. It would be interesting to investigate how Asian diet affects the composition of Asian fat and the "freezing" of such adipose tissue.

All our subjects experienced transient pain and numbness. We have identified that as subjects were asked to recall such adverse effects and the length they took to subside, there would be some degree of inaccuracy but all symptoms were temporary. Although there was numbness for up to 3 weeks, the sensory function was not affected permanently. This is supported by a study by Coleman et al. [17] where they assessed the sensory function by neurological evaluation in 9 subjects and biopsies for nerve staining in 1 subject after cold exposure. Transient reduction in sensation occurred in 6 of the 9 subjects assessed by neurologic evaluation. Sensation returned within 7 weeks post-treatment (with a mean of 3.6 weeks). Biopsies showed no long-term change in nerve fiber struc-

TABLE 2b. Summary of Caliper Readings of Love Handle for Group B

	No. of treatment cycles	Mean	SD	*P*-value
Love handle, treatment site (no. of subjects = 6)				
Caliper readings at baseline	12	30.8	4.2	0.003
Caliper readings 2 months post-treatment	12	26.7	4.4	
Caliper readings pre-second treatment	12	27.7	7.2	0.084
Caliper readings 2 months post-second treatment	12	26.5	6.9	
Love handles, control site (no. of subjects = 6)				
Caliper readings at baseline	10	19.8	6.9	0.721
Caliper readings 2 months post-treatment	10	19.2	7.0	
Caliper readings pre-second treatment	10	22.9	9.0	0.878
Caliper readings 2 months post-second treatment	10	23.3	10.5	

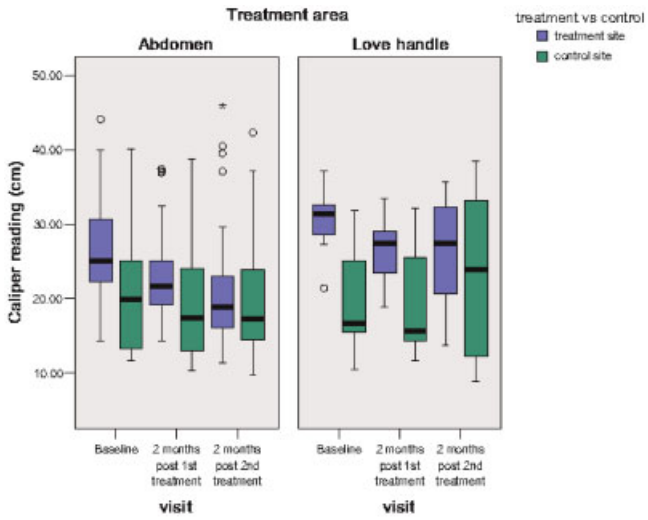

Fig. 6. Boxplot of caliper readings at treatment and control site (Group B).

ture. Ischemia times shorter than 1 hour typically are associated with recovery of function, whereas 3 hours or more may result in permanent damage [18]. This means that the intensity of cold exposure and time used for the cryolipolysis effect is below the threshold for significant nerve damage. There have been several cases reported where patients experienced severe, persistent pain, for at least several weeks. The cause is not yet known but could be related to inflammatory changes in the fascia, nerves, or the fat itself. This is still under investigation and physicians should be aware of these symptoms and may require medication.

CONCLUSION

The use of non-invasive cryolipolysis is effective for fat layer reduction in Chinese. There are temporary adverse effects, such as redness, bruising, and numbness that resolve spontaneously. A subsequent treatment leads to further reduction in fat thickness but the efficacy seems to be lower. The second treatment was statistically significant in the abdomen but not the love handles. This can be further investigated with small applicators now available commercially.

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