ORIGINAL ARTICLE

Could Kinesio tape replace the bandage in decongestive lymphatic therapy for breast-cancer-related lymphedema? A pilot study

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Abstract

Goals of work The purpose of this study is to compare the treatment and retention effects between standard decongestive lymphatic therapy (DLT) combined with pneumatic compression (PC) and modified DLT, in which the use of a short-stretch bandage is replaced with the use of Kinesio tape (K-tape) combined with PC.

Materials and methods Forty-one patients with unilateral breast-cancer-related lymphedema for at least 3 months were randomly grouped into the DLT group (bandage group, N=21) or the modified DLT group (K-tape group, N=20). Skin care, 30-min manual lymphatic drainage, 1-h pneumatic compression therapy, application of a short-stretch bandage

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Physical Therapy Center, National Taiwan University Hospital, No. 7, Chun-Shan S. Rd., Taipei, Taiwan, Republic of China or K-tape for each group, and a 20-min physical therapy exercise were given during every treatment session. Patient evaluation items included physical therapy assessment, limb size, water composition of the upper extremity, lymphedema-related symptoms, quality of life, and patients' acceptance to the bandage or tape.

Main results There was no significant difference between groups in all outcome variables (P>0.05) through the whole study period. Excess limb size (circumference and water displacement) and excess water composition were reduced significantly in the bandage group; excess circumference and excess water composition were reduced significantly in the tape group. The acceptance of K-tape was better than the bandage, and benefits included longer wearing time, less difficulty in usage, and increased comfort and convenience (P<0.05).

Conclusions The study results suggest that K-tape could replace the bandage in DLT, and it could be an alternative choice for the breast-cancer-related lymphedema patient with poor short-stretch bandage compliance after 1-month intervention. If the intervention period was prolonged, we might get different conclusion. Moreover, these two treatment protocols are inefficient and cost time in application. More efficient treatment protocol is needed for clinical practice.

Keywords Breast-cancer-related lymphedema · Bandage · Taping · Decongestive lymphatic therapy

Introduction

One of every four breast cancer patients suffers from lymphedema [16]. Breast-cancer-related lymphedema is one of the complications that results after breast cancer treatment. It is defined as arm edema in the breast cancer



patient caused by interruption of the flow of the axillary lymphatic system from surgery or radiation therapy, which results in the accumulation of fluid in the subcutaneous tissue of the arm, with a decrease in tissue distensibility around the joints and an increased weight of the extremity [2]. Breast-cancer-related lymphedema may have a physical, psychological, and functional impact, and it increases the risk of repeated episodes of superficial infection [8, 18, 19, 22]. It is worthy to place importance on the intervention of breast-cancer-related lymphedema.

Decongestive lymphatic therapy (DLT) is a common management for lymphedema. A program combining skin care, manual lymphatic drainage, exercise, and compression therapy (multilayer bandage or garment) is recognized as the best practice in lymphedema management. There have been numerous prospective investigations with different treatment frequency and duration showing the effect of DLT [1, 4, 13-15, 20, 21, 24]. Under the consideration of personal and medical resources in clinical practices, pneumatic compression (PC) as a supplemental therapy is often given to patients to improve the effectiveness of DLT [20]. It is a mechanical method of delivering compression to swollen limbs, often combined with DLT to treat patients with breast-cancer-related lymphedema [3]. PC has been accepted as a standard supplemental therapy in Taiwan for many years.

A multilayer bandage can only be stretched a little and is usually used to maintain the volume reduction from manual lymphatic drainage. It provides mild pressure during resting and creates higher pressure during muscle contraction to prevent skin extension. The lymphatics are compressed between the muscle and the bandage, causing them to be manually pumped. The variable pressure over the skin created by muscle contraction is identical to the effect obtained after a massage, which increases the lymph flow. The bandage should be kept on as long as possible, even during the night [5, 14, 17, 25]. Unfortunately, patients in Taiwan have poor compliance with using a short-stretch bandage due to the hot and humid conditions. Insufficient application time will limit the treatment effect.

Kinesio tape (K-tape) for lymphatic drainage is a new choice in the field of physical therapy. The material used for the Kinesio tape and the original concept of the taping technique was introduced by Dr. K. Kase in 1973. K-tape had been designed to allow 30~40% longitudinal stretch. It is composed of 100% cotton fibers and acrylic heat sensitive glue. Development of the technique for its administration is still ongoing. Dr. Kase claimed that applying K-tape would have physiological effects including decreasing pain or abnormal sensation, supporting the movement of muscles, removing congestion of lymphatic fluid or hemorrhages under the skin, and correcting misalignment of joints. After applying K-tape, the taped

area will form convolutions to increase the space between the skin and muscles. Once the skin is lifted, the flow of blood and lymphatic fluid is promoted [9–11]. Other advantages are that a patient can take a shower without taking the tape off since it is waterproof. Patients can wear it 1 to 3 days and even longer if it is applied on the back or buttock area. Many practitioners use it in clinical practice in Taiwan, and it has a beneficial effect. However, there is insufficient evidence for its clinical effects on lymphedematic limbs.

The purpose of this study is to compare the treatment effect between traditional DLT combined with PC and modified DLT with PC, in which the bandage was replaced with K-tape.

Materials and methods

The study protocol was approved by the hospital ethics committee, and all participants provided written consent.

Research design

The study used a randomized, single-blinded, controlled design. Participants were randomized into two study groups: the decongestive lymphatic treatment group (DLT group; bandage group) and the modified decongestive lymphatic treatment group (modified DLT group; K-tape group). Sealed envelopes were prepared, and patients randomly chose one in order to be assigned to a group. The assignment was by block, with block size being 4. Each subject went through a 4-week control period, a 4-week intervention period, and was followed up for 3 months so that the retention effect of the treatments could be studied. There was no intervention during the 4-week control period (the first month). The treatment programs were given during the 4-week intervention period (the second month).

Subjects

A subject database was gathered from social workers around the Taipei area in hospitals, foundations, and associations, which are devoted to serving patients after or during breast cancer treatment. Subjects who fulfilled the following criteria were eligible for the study: (1) unilateral breast-cancer-related lymphedema for at least 3 months, (2) moderate to severe lymphedema (circumference of affected limb greater than that of the sound limb by at least 2 cm at one or more measurement points), (3) good compliance and willingness to sign the written consent form.

The exclusion criteria were as follows: (1) active cancer or disease that might lead to swelling and presently taking diuretic therapy or other lymphedema-influencing drugs,



(2) port-A catheter with adhesion on the chest wall of the affected side, (3) skin disease, (4) irremovable bracelet or ring, (5) marked restriction of active range of motion in the affected upper extremity.

Treatment interventions

Treatment intervention was given during the 4-week intervention period. The bandage group received DLT combined with PC every treatment session, which included skin care, 30-min manual lymphatic drainage, 1-h pneumatic compression therapy (at 40 mm Hg), application of a short-stretch bandage, and a 20-min physical therapy exercise. The tape group also received DLT combined with PC, but a K-tape was used instead of a bandage. Each group was treated 2 h per session, five sessions per week in the 4-week intervention period. Four physical therapists (PTs) provided treatment. The program was standardized, with each PT following the same protocol for lymphatic drainage to the anterior trunk, posterior trunk and affected arm, always moving fluid from the affected side toward the unimpaired side. The 20-min exercise regimen included self-lymphatic drainage, relaxation and breathing exercises, and an exercise designed for lymphedematic patients that increases the active range of motion in the trunk and upper extremities [12, 13]. After lymphatic drainage and before doing the exercises, either the short-stretch bandage or the K-tape was applied by the physical therapist. The patients were instructed to "use the short-stretch bandage/K-tape as long as possible". Patients or their families in the bandage group were taught how to properly apply the bandage.

During the follow-up phase, patients in both groups were instructed to maintain skin care, self-lymphatic drainage, exercise, and to replace the bandage/K-tape with a compression garment.

Assessments and outcome measures

There were four evaluations, which were executed before and after the control period, after the intervention period, and after the 3-month follow-up. Baseline and demographic data were recorded for each subject at the first evaluation, including surgery type, number of excised lymph nodes, history of radiotherapy and chemotherapy, post-operative duration, lymphedema duration, previous treatment, etc. (Table 1). A well-trained PT who was blind to the groupings evaluated all the subjects.

Primary end points

Limb size

Water-displacement volumetric measurements and circumference measurements were used to quantify limb size at each evaluation. Each limb was immersed in a water-filled tank. The displaced fluid was collected and measured. The circumference of both arms was measured, starting at the wrist, with repeated measurements every 3 cm proximally to the axilla. According to our prior study, the inter- and intra-rater reliability of water-displacement measurements and circumference measurements were both high (r=0.99) [6, 23].

Table 1 Comparison of details of patients in the bandage group and the K-tape group

| | Bandage $(n=21)$ | K-tape $(n=20)$ |
|--------------------------------------|----------------------|------------------------|
| Surgery type | | |
| Radical mastectomy | 1 (4.8%) | 1 (5%) |
| Modified radical mastectomy | 15 (71.4%) | 17 (85%) |
| Simple mastectomy | 2 (9.5%) | 1 (5%) |
| Breast conservation | 3 (14.3%) | 1 (5%) |
| Number of dissected lymph nodes | 17.7±5.4 (4~26) | 18.2±11.4 (1~52) |
| Subjects underwent radiotherapy | 17 (81.0%) | 17 (85%) |
| Average dose of radiotherapy (cGy) | 3890±2342.3 (0~6000) | 4276.2±2078.7 (0~6000) |
| Subjects underwent chemotherapy | 19 (90.5%) | 20 (100%) |
| Post-op duration (months) | 64.6±58.6 (7~241) | 57.5±44.6 (5~166) |
| Lymphedema duration (months) | 27.4±29.6 (3~124) | 41.2±42.0 (6~160) |
| Previous treatment | 19 (90.5%) | 19 (95%) |
| Hardness | 5.5±7.0 (0~22) | 4.9±6.1 (0~25) |
| Lymphedema on dominant side | 13 (61.9%) | 9 (45%) |
| Concurrent treatment | 4 (19%) | 4 (20%) |
| Exercise compliance | 1.8±0.4 (1~2.3) | 1.8±0.4 (0.5~2.6) |
| Number of wounds during intervention | $0.1\pm0.3~(0\sim1)$ | 0.2±0.5 (0~2) |



Secondary end points

Water composition of the upper extremity

An eight-polar tactile-electrode impedance meter (Inbody 3.0, Biospace, Seoul, Korea) was used in the water composition analysis. Resistance (*R*) of the arms, trunk, and legs were measured, respectively.

Lymphedema-related symptoms

Researchers have highlighted lymphedema with various physiological symptoms. Although there is no instrument currently validated to measure these changes, Williams et al. used 11 lymphedema-related symptoms to evaluate the effects of intervention [24]. Our outcome variables were revised from Williams' study after discussion with seven lymphedema patients and three experienced physical therapists. The final target symptoms chosen in this study were tightness, heaviness, pain, hardness, soreness, discomfort, heat, fullness, tingling, weakness, and numbness. These symptoms were assessed by a visual analog scale (VAS) from 0 to 10 (0=none and 10=worst possible). To avoid neglecting any lymphedema-related symptom, three blank items and accompanying scales were provided.

Health-related quality of life

There is no condition-specific quality of life tool available for lymphedema. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 and QLQ-BR23) is an internationally recognized instrument for the assessment of quality of life in breast cancer patients and has been administered in breast-cancer-related lymphedema studies [1, 24]. The Taiwan Chinese Version of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires used in this study already had their reliability and validity established [7], and permission to use the instruments was obtained. Fifty-three questions were assigned to 23 scales, including one global health-related quality of life scale, nine functional scales (physical, role, emotional, cognitive, social, body image, sexual functioning, sexual enjoyment, and future perspective), five symptom scales (fatigue, pain, breast symptoms, arm symptoms, and nausea and vomiting), and eight single items. A higher score in global health status and functional scales indicates a better health status, whereas a lower score in symptom scales and single items indicates a better health status.

Subjects' response to bandage or K-tape

The compliance of subjects in each group was measured by recording the length of time the bandage or K-tape was

worn daily and the daily frequency of self exercise during the intervention period. At the third evaluation, the difficulty, discomfort, and inconvenience of using either the bandage or K-tape were evaluated by employing a VAS from 0 to 10 (0=none and 10=worst possible). The frequency of itching or irritation and the number of wounds that developed due to bandage or K-tape use (side effect wound development) were recorded.

Data reduction and statistical analysis

The excess limb volume, circumference, and water composition were derived by taking the difference between the healthy side and affected side. The average of the excess circumference was calculated as the sum of excess measured circumferences divided by n (n=the number of measured circumference). The QOL score was calculated with the transformation formula provided by the EORTC OLO-C30 Scoring Manual.

The total treatment effects in the control period and intervention period of each group in all outcome variables were calculated as follows: $\Delta \text{control} = \text{the data change}$ during the control period (|data from 2nd evaluation-data from 1st evaluation|); $\Delta \text{intervention} = \text{the data change during}$ the intervention period (|data from 3rd evaluation-data from 2nd evaluation|); total treatment effect= $\Delta \text{intervention}$ - $\Delta \text{control}$. The assumption of this calculation was that if there was no intervention, the spontaneous change (the dotted line) during the second month would follow the trend as during the first month. Therefore, we tried to measure the actual change made by the intervention (Fig. 1).

The independent two sample t test, the Mann–Whitney U test, and the chi-square test were used to analyze the differences of all the confounding factors, outcome variables at baseline, total treatment effect, and retention effect between the two groups. The Friedman test was used to test the difference of all outcome variables at baseline, after the control period, after intervention, and at follow-up within the groups. The level of statistical significance was set at 0.05. All the estimated P values were two-tailed.

Sample size estimation

Using our outcome data, setting α =0.05 and power=0.8, the sample size was estimated. It needs 228 subjects in one group to reach significant difference.

Results

Forty-two subjects who fulfilled the criteria were randomized to the bandage group or the K-tape group, and each group had 21 subjects. One woman who was randomized to



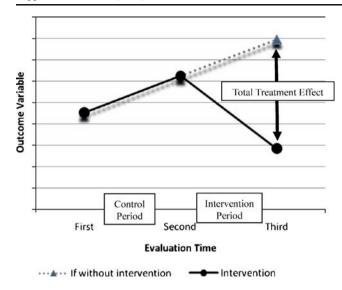


Fig. 1 Hypothetical illustration of the progression of lymphedem

the tape group withdrew from the study after 1 week of intervention because of anemia and hospitalization (Fig. 2). The rest completed the whole trial, including the follow-up.

The average age of the patients was 54.6 years (range from 36 to 75). There were no statistically significant differences in baseline clinical data (Table 1) and outcome variables at the first evaluation (Table 2) except financial difficulty in QLQ-C30 (P=0.011).

During the control period, all of the outcome variables maintained stability except for the average circumference difference of the forearm and the symptom of hardness in the tape group, which significantly worsened (P<0.05).

The total treatment effect of excess limb size in the bandage group and the tape group, as measured by water displacement, was 84.0 ml and 51.3 ml, respectively. The total treatment effects of excess volume, excess circumference, water composition, 11 lymphedema-related symptoms, and 23 items indicate that there was no statistically

significant difference in the quality of life between the two groups (Tables 2 and 3). After the 3-month follow-up, there was also no difference between the two groups except the emotional function in QLQ-C30 improved in the bandage group and deteriorated in the K-tape group (P<0.05).

In the bandage group, the excess limb size and excess water composition reduced significantly after the intervention period, and a significant decrease in the circumference of the lower part of the upper arm was seen, but not the upper part. However, in the tape group, only excess circumference of the forearm and excess water composition reduced significantly (Table 2); there also was a significant improvement in the role function of QOL in the tape group after intervention. In Table 3, we present the three most common symptoms of patients in our study, including fullness (93.5%), tightness (92.7%), and discomfort (89.4%). Four out of 11 symptoms in the bandage group (tightness, soreness, discomfort, and fullness) and six out of 11 symptoms in the tape group (tightness, pain, hardness, discomfort, fullness, tingling) were significantly relieved (P<0.05) after the intervention period. After the 3-month follow-up, three symptoms (tightness, heaviness, and weakness) became significantly worse in the bandage group. The scores for future perspectives in the QLQ-C30 for both groups also decreased significantly (P < 0.05).

The acceptance of K-tape was better than the bandage, and patients reported using the K-tape longer, with a greater ease of use, and increased comfort, and convenience in daily activities. However, there were more wounds that occurred for those in the K-tape group (Table 4).

Discussion

Using our outcome data to estimate the sample size, it needs 228 subjects in one group to reach significant difference. Small sample size is one limitation of this pilot

Fig. 2 Flow chart

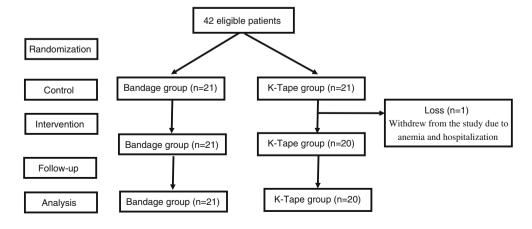




Table 2 The total difference in excess limb size and water composition between the bandage and K-tape groups

| | | Bandage group | | | | | | | | | K-tape group | | | | | | | | |
|------------|---------------|----------------|------------------|---------|------------------|------------|-------------------|---------|-------|-----------|-------------------|---------|-------------------|------------|---------------|----------|-----------|--|--|
| | | Control period | | | Intervent | ion period | Follow-up period | | | | Control 1 | period | Intervent | ion period | Follow-u | p period | | | |
| | | 1st evalu | uation 2nd evalu | | uation 3rd evalu | | ation 4th evaluat | | ation | 1st evalu | valuation 2nd eva | | luation 3rd evalu | | uation 4th ev | | raluation | | |
| | | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD | | |
| Water disp | lacement (ml) | 513.7 | 262.2 | 511.9 | 262.7 | 426.0* | 215.5 | 448.6 | 231.0 | 505.3 | 312.9 | 522.5 | 346.0 | 488.4 | 316.8 | 491.4 | 353.2 | | |
| Circumfere | nce (cm) | 2.77 | 1.64 | 3.09 | 1.42 | 2.66* | 1.26 | 2.62 | 1.53 | 2.68 | 1.37 | 2.96 | 1.64 | 2.81 | 1.60 | 2.83 | 1.72 | | |
| Upper | Upper | 2.07 | 1.44 | 2.23 | 1.58 | 2.44 | 1.70 | 2.03 | 1.75 | 2.03 | 1.36 | 2.29 | 1.57 | 2.80 | 2.32 | 2.23 | 1.67 | | |
| Arm | Lower | 3.75 | 2.31 | 3.88 | 1.93 | 3.19* | 1.82 | 3.34 | 1.98 | 3.71 | 1.84 | 3.99 | 1.97 | 3.90 | 2.00 | 4.00 | 1.94 | | |
| Forearm (| cm) | 2.75 | 1.87 | 3.23 | 1.52 | 2.58* | 1.23 | 2.61 | 1.61 | 2.58 | 1.75 | 2.86* | 2.01 | 2.55* | 1.89 | 2.64 | 2.10 | | |
| Water com | position (l) | 0.436 | 0.315 | 0.401 | 0.277 | 0.328* | 0.231 | 0.321 | 0.253 | 0.386 | 0.342 | 0.375 | 0.312 | 0.315* | 0.287 | 0.310 | 0.318 | | |

SD standard deviation

Table 3 The total difference in lymphedema-related symptoms between the bandage and K-tape groups

| | Bandage g | group | | | | | | K-tape group | | | | | | | | |
|------------|----------------|-------|-----------------------|-------------|----------------------|------|----------------|--------------|----------------|------|---------------------|------------------|------------------|-------------------|---------|------|
| | Contro | | ol period | tion period | Follow-up period | | | | Control period | | Intervention period | | Follow-up period | | | |
| | 1st evaluation | | evaluation 2nd evalua | | ation 3rd evaluation | | 4th evaluation | | 1st evalua | tion | 2nd evalua | uation 3rd evalu | | tion 4th evaluati | | tion |
| | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD | Average | SD |
| Fullness | 4.45 | 3.73 | 4.39 | 3.50 | 2.25* | 2.51 | 3.25 | 2.84 | 4.93 | 3.49 | 3.33 | 2.78 | 2.24* | 2.05 | 2.93 | 2.36 |
| Tightness | 4.40 | 3.59 | 4.50 | 3.38 | 2.31* | 2.38 | 4.19* | 2.64 | 4.93 | 2.51 | 4.14 | 2.72 | 2.56* | 2.35 | 3.41 | 2.53 |
| Discomfort | 4.38 | 3.79 | 3.47 | 3.37 | 1.89* | 2.56 | 3.18 | 2.88 | 4.39 | 3.25 | 3.69 | 2.36 | 1.35* | 1.65 | 2.47 | 2.44 |

SD standard deviation

^{*}P<0.05, statistically significant difference compared to the previous evaluation result

^{*}P<0.05, statistically significant difference compared to the previous evaluation result

Table 4 Subjects' responses to the bandage or K-tape

| | Bandage | K-tape | P value |
|--|-----------------|-----------------|----------|
| Day usage (h) | 7.8±3.7 | 15.1±1.6 | < 0.0005 |
| Night usage (h) | 6.0 ± 2.0 | 6.9 ± 1.9 | 0.157 |
| Discomfort | 4.11 ± 3.11 | 1.33 ± 2.28 | 0.001 |
| Difficulty | 3.21 ± 3.03 | 0.66 ± 2.00 | < 0.0005 |
| Inconvenience | 5.32 ± 3.15 | 0.91 ± 1.81 | < 0.0005 |
| Itch | 1.8 ± 4.4 | 2.2 ± 2.8 | 0.293 |
| Wound development from usage (side effect) | 0.05 ± 0.22 | 0.55 ± 0.83 | 0.013 |

study. On the other hand, this might imply there was no significant difference of total treatment effect between the two groups after 1-month intervention. This suggests that K-tape could replace the bandage in DLT and could be an alternative for patients with breast-cancer-related lymphedema who had poor compliance with the bandage. Within the groups, patients in both groups experienced improvement in some of the outcome variables.

Good retention effects in most of the outcome variables were found, except that three symptoms in the bandage group significantly worsened after the follow-up period. Only the emotional function QOL score showed a significant difference between the groups after the follow-up. The emotional function score in subjects of the bandage group improved, but significantly worsened in the tape group. During the intervention period, subjects in the bandage group frequently complained that wearing a bandage was very inconvenient, and it served as a reminder to them that they were sick and handicapped. After substituting a compression garment for the bandage in the follow-up period, they might feel much better. On the contrary, for patients in the tape group, they had to wear a compression garment instead of the relatively more comfortable K-tape. This might cause them to feel uncomfortable. The significantly reduced future perspective in both groups during the follow-up period might have been due to a lack of support and care from PTs in the follow-up period.

DLT is a common management for lymphedema, and many studies aimed to measure its effectiveness [4, 13–15, 21]. Most intervention studies were of quasi-experimental design because of ethical consideration. A real control group could not exist. No control study will overlook the spontaneous change during the study period. This spontaneous change may accompany the progress of lymphedema with time or other confounding factors. This study incorporated a control period and tried to minimize the effect of this spontaneous change. The statistical procedure of this study also followed this assumption. However, generalization of our results should be conservative. No clinical evidence has supported the assumption that the spontaneous change would continue through time.

Limited duration of bandage use may limit the effectiveness of DLT. Subjects in the bandage group only used the bandage for an average of 7.8 h during the day (it was supposed to be 16 h). The climate in Taiwan and any arising need to re-apply the bandage were the main reasons for limited usage. The hot and humid climate prohibited most patients from tolerating the bandage unless they were in an air-conditioned room. Moreover, subjects in the bandage group or their family had to learn the bandage technique so that they could re-bandage after taking a bath or after activities that resulted in removal of the bandage. A significantly higher VAS score in discomfort, inconvenience, and difficulty might confirm this. That is why we searched for an alternative to the bandage.

Although the mechanism for the treatment effect resulting from the use of K-tape is not clear, this tape is generally applied in clinical practice in Taiwan. After applying Ktape, the taped area would form convolutions when adjacent joints move. Physical therapists using K-tape believe that the convolutions increase the space between the skin and muscles and thus promote the flow of blood and lymphatic fluid [9-11]. Using the tape is more comfortable and convenient due to its skin-like and waterproof characteristics. However, the present study found that there were more wounds caused by the use of tape than bandages. K-tape was applied by PTs but could be removed by the subjects themselves once they were taught the special technique to remove it. Removal of the tape from the skin is a two-handed activity, and our subjects usually peeled off the K-tape with the sound hand by themselves without any help. This might be the reason why there were a greater number of wounds in the tape group.

The cost of materials in the bandage group and tape group was similar in our 1-month intervention period. If the application period extended to more than 1 month, the cost of K-tape was higher than bandages because the K-tape is a one-use product, but the bandage can be reused. A cost-effectiveness analysis might be considered in clinical practice.

Conclusion

When comparing the use of a bandage versus K-tape in breast-cancer-related lymphedema patients who received DLT combined with PC, the study results suggest that K-tape could replace the bandage for patients who had poor compliance with bandage use after 1-month intervention. If the intervention period was prolonged, we might get a different conclusion. Moreover, these two treatment protocol are inefficient and time cost in application. More efficient treatment protocol is needed for clinical practice.



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