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Can Lymph Transportation Capacity Predict Treatment Efficacy of Lower Extremity Lymphedema by LVA?

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Summary: Treatment outcomes for lower extremity lymphedema (LEL) using multiple lymphaticovenular anastomoses (LVA) are still uncertain. Classification of progression of lymphedema by disease staging is a potential preoperative predictor of the efficacy of treatment, but it is difficult to judge progression of lymphedema objectively. Recent studies have indicated that lymph pump dysfunction, which reflects lymph transportation capacity, is associated with lymphedema progression. Indocyanine green (ICG) lymphography, a minimally invasive modality for pathophysiological assessment of lymphedema, can be used for rapid and objective measurement of ICG velocity (ICGv) and transit time to the knee (TTk), which are parameters of lymph transportation capacity, over a certain period. In the current study, we analyzed the relationship between these parameters and outcomes for LEL treated by multiple LVA. Thirty-four consecutive patients who underwent multiple LVA and ICG lymphography were enrolled in the study. The relationship of ICGv and TTk with the efficacy of treatment by LVA (LEL index reduction) was investigated using Pearson correlation coefficient analysis. LEL index reduction was more strongly correlated with ICGv than with TTk, whereas it was weakly correlated with both quantification methods of lymph pump function ($r > 0.6$). Both ICGv and TTk are objective and simple parameters that can measure lymph pump functions quickly. Lymph pump function, especially calculated with ICGv, might help predict the treatment efficacy and objective evaluation after therapeutic intervention using multiple LVA. *(Plast Reconstr Surg Glob Open 2021;9:e3342; doi: 10.1097/GOX.0000000000003342; Published online 3 February 2021.)*

INTRODUCTION

Surgical treatment of lymphedema with lymphatic venous anastomosis (LVA) has become a standard method. However, treatment outcomes for lower extremity lymphedema (LEL) using multiple LVA are still unpredictable.[1,2] In some advanced cases, this surgery may be ineffective due to lymph pump dysfunction and it is challenging to determine the optimal surgical indication. Besides lymph circulation, lymph pump function is a crucial factor for lymphedema evaluation.[3,4] Lymphatic pump function is reported to be influenced by the intrinsic properties of lymphatic muscle and the regulation of pumping by lymphatic load, spontaneous contraction rate, contractility, and neural influences. Lymphatic dysfunction and defects can be a common pathogenesis of lymphedema among pathologies that directly involve the lymphatic system.[5,6]

The ICG velocity (ICGv) proposed by Yamamoto et al. in 2013[7] and the transit time (TT) suggested by Unno et al in 2010[8] are intriguing concepts that allow simple quantification of lymph pump function within a specified period. Using these scales, even inexperienced therapists can measure potential lymphatic function. To date, we have measured ICGv, TTk for 5 minutes, and the LEL index before and after surgery in 34 patients treated with LVA at 3 or more sites. Here, to investigate whether these indexes for lymphatic vessel function can predict the efficacy of treatment with LVA, we analyzed the correlation of each index with the treatment outcome for LEL.

METHODS

From July 2015 to June 2019, 34 consecutive patients who underwent multiple (more than 3) LVA and ICG

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$$\text{LEL index reduction}(\%) = \left[1 - \frac{(\text{before LEL index}) - (\text{after LEL index})}{\text{after LEL index}}\right] \times 100$$

Fig. 1. Formula for calculating the LEL index reduction (%).

lymphography were enrolled in the study. Inherited lymphedema cases were excluded. ICGv and TTk were measured 1 month before surgery and 6 months after surgery.[7,8] Briefly, 0.3 ml of ICG (0.5%) was injected subcutaneously at the dorsal web between the base of the first and second toes. Subsequently, ICG dye movement from the injection site was traced by visualizing its fluorescence signal under a conventional fluorescence mode with an infrared light camera. (Photodynamic Eye neo; Hamamatsu Photonics K.K., Hamamatsu, Japan). ICGv was calculated by dividing the distances between the injection point and the most proximal position of the dye at 5 minutes after ICG injection. Transit times were defined as the time required for ICG uptake to the knee (TTk). The LEL index was calculated by dividing the sum of the squares of the circumferences at 5 sites in the lower limbs by the body mass index. The LEL index reduction (%), which reflects the efficacy of LVA treatment, was calculated as the percentage reduction of the LEL index after surgery compared with that before surgery. Pearson correlation coefficient analysis was used to evaluate the relationships of LEL index reduction with ICGv and TTk (Figs. 1 and 2).

RESULTS

Patients' International Society of Lymphology stages by limb were stage 0 in 3 limbs, stage I in 7, stage II in 10, and stage III in 14. Examinees' age ranged from 25 to 76 years (average, 51.3 years), and body mass indices ranged from 18.3 to 29.8 kg/m^2 (average, 24.71 kg/m^2). There was no case in which ICG reached the groin or failed to reach the knee within 5 min after dye injection. ICGv and TTk ranged from 2.0 to 10.2 cm/min (average, 5.2 cm/min) and from 9.0 to 45.0 min (average, 23.6 min), respectively. The LEL index reduction was more strongly correlated with ICGv (Pearson correlation coefficient r = 0.673, 95% confidence interval: 0.434 to 0.824, R^2: 0.453) than with TTk (r = –0.603, 95% confidence interval: –0.782 to –0.334, R^2: 0.364), whereas it was weakly correlated with both quantification methods of lymph pump function (r > 0.6) (Table 1).

DISCUSSION

Measurement of the limb circumference is the most commonly used method for evaluating extremity lymphedema. However, comparison among different patients is difficult using this measurement because the lower-limb circumference varies depending on the physique of the patient and is easily affected by changes in body weight. The LEL index, which was introduced by Yamamoto et al,[9] is easily obtained from body measurements and is highly correlated with clinical stage in patients, which suggests its potential use as a severity scale. The LEL index also allows a more objective assessment of the severity of lymphedema through a numerical rating, regardless of the body type. The rate of reduction of the LEL index after surgery compared with that before surgery more strictly reflects the efficacy of treatment by multiple LVA.

The degree of clinical progression of lymphedema pathology cannot be judged simply by the circumference

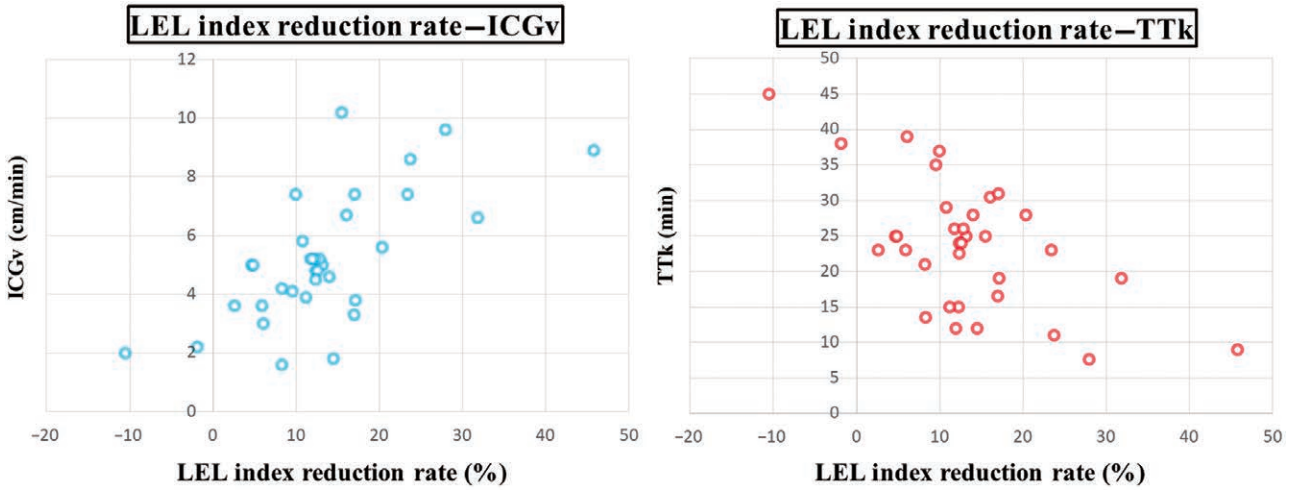

Fig. 2. Scatter plots of LEL index reduction rate vs ICGv and TTk. Weak associations were found across all patients.

Table 1. Mean Value and SD of Each Parameter

	Preop LEL Index	Preop LEL Index	LEL Index reduction rate (%)	ICGv (cm/min)	TTk (min)
Mean	326.5	281.4	13.3	5.17	23.6
SD	75.1	56.0	9.83	2.16	8.96

of the foot. Dermal backflow patterns using ICG lymphography are often used for judgment of clinical progression and for preoperative prediction of the efficacy of LVA treatment.[10] However, these patterns are not easy to quantify and experience is needed to make a subjective judgment. A further problem is the time required for contrast to make a more accurate diagnosis.[10] We have focused on TTk and ICGv, which are more objective and straightforward parameters that can be used to measure lymph pump function in a shorter time. There are 2 defined transit times: TTk, the transit time to the knee; and TTg, the transit time to the groin. Because TTg is long and some cases requires >2 hours for measurement, it is impractical for use; thus, only TTk was used in this study. Both TTk and ICGv had a weak correlation with LEL index reduction. ICGv had a shorter average measurement time compared with TTk and a slightly stronger correlation with LEL index reduction, which suggests that ICGv may be a more accurate predictor of therapeutic effect.

We note that the correlation coefficient with LVA for lymphedema treatment effect was only about 60% and more for each parameter. In both measurements, there were cases in which the contrast agent entered the deep layer, and detection of the signal was difficult at the central tip of the image in a relatively short time. The reliability of data collected in such cases is decreased and this may affect the results to an extent. If detection methods can be improved, ICGv in particular may be expected to be a more powerful predictive tool for therapeutic effects, compared with the time-consuming classification of dermal backflow patterns.

In conclusion, the lymph pumping function that objectively measured in a short time using either ICGv or TTk had a weak correlation with LEL index reduction. These scales, especially calculated as ICGv, might help predict the treatment efficacy and objective evaluation after therapeutic intervention using multiple LVA.

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