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THE USE OF BIOIMPEDANCE SPECTROSCOPY TO MONITOR THERAPEUTIC INTERVENTION IN PATIENTS TREATED FOR BREAST CANCER RELATED LYMPHEDEMA

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ABSTRACT

We performed a multi-institutional analysis to evaluate the ability of bioimpedance spectroscopy (BIS) to capture the impact of lymphedema treatment compared with observation alone in the management of breast cancer related lymphedema (BCRL). We utilized a retrospective review of 50 patients with breast cancer who were evaluated with BIS at baseline and following loco-regional treatment. An analysis was performed comparing changes in L-Dex scores for those patients undergoing treatment for BCRL (n=13) versus those not undergoing intervention (n=37). A second (subset) analysis was also performed on all patients with elevated L-Dex scores compared to baseline prior to undergoing loco-regional treatment (n=32). When comparing the cohort treated for BCRL to those not treated, L-Dex scores were significantly reduced (-4.3 v. 0.1, p=0.005) in the period following intervention (for treated patients). For the subset of patients with elevated L-Dex scores post-operation, the change in L-Dex score following BCRL treatment was significantly reduced (-5.8 v. 0.1, p=0.001) compared with the group observed that had elevated post-surgical L-Dex scores. In this analysis, BIS was able to detect early onset lymphedema and subsequently significant changes (reductions) in L-Dex scores directly related to intervention for BCRL compared with observation alone.

Keywords: bioimpedance spectroscopy, breast cancer, lymphedema, early detection, subclinical assessment

As changes in the optimal loco-regional and systemic management of breast cancer have evolved over the past several decades, women diagnosed with the disease have experienced improved long-term outcomes (1). As a direct result of these advances in treatment, a greater number of long-term survivors now exist than in the past. These patients provide a gateway to an understudied and poorly understood part of breast cancer treatment, namely the long term sequelae of breast cancer therapies. Loco-regional treatments (i.e., operation, radiation therapy) can be associated with long term complications including changes in breast appearance (telangiectasias, fibrosis, and volume loss), decreased arm range of motion, chronic pain, and breast cancer related lymphedema (BCRL). BCRL represents a major long term complication of treatment; however, new diagnostics and treatment paradigms for the management of this condition remain limited (2,3).

BCRL typically begins as a sub-clinical process and over time can develop into a clinically apparent condition (3). Prior to the development of clinically visible arm swelling, there is a period of increased extracellular fluid that represents the early stages of the disorder (3). Similar to other disease processes, this early phase may provide a period where intervention is more effective and could limit progression to the chronic phase of BCRL and its sequelae (persistent swelling, infections, decreased range of motion). Unfortunately, minimal data are available on the topic of early intervention.

Recently, however, a prospective study from the National Institutes of Health did find that treatment following early detection was associated with a subsequent reduction in arm volumes and a decrease in the need for further treatment (4). Two randomized trials have also been performed to evaluate this concept with one study finding an 18% reduction in BCRL with early intervention at one year and a second study finding a 19% reduction at two years, despite the fact that these studies did not use newer BCRL diagnostics (5,6).

Bioimpedance spectroscopy (BIS) is a valuable diagnostic tool for assessment of extracellular fluid accumulation and BCRL in particular. One key to BIS is its ability to detect subclinical extracellular fluid accumulation, allowing for early BCRL detection and treatment (7,8). The feasibility of implementation and sensitivity of BIS have been previously documented (9); however, limited data exist evaluating the ability of BIS to be utilized for early detection and for following early treatment of BCRL. Therefore, the purpose of this study was to perform an exploratory analysis of multi-institutional data to determine if, in clinical settings, BIS can detect changes in extracellular fluid volume following 1) breast cancer treatment and 2) in response to treatment of early onset BCRL.

MATERIALS AND METHODS

Three centers that had experience with the L-Dex U400 (ImpediMed Limited, Brisbane, Australia) provided retrospective data from patients who received L-Dex procedures. Collection of data and subsequent analyses were approved at each institution via an institutional review board. This analysis represents medical record data from 50 patients who were prospectively treated according to the standard of care for their breast cancer diagnoses.

Patients were included if they 1) had a diagnosis of breast cancer; 2) were at least 18 years of age and underwent operation (lumpectomy or mastectomy) with unilateral sentinel lymph node (SLN) biopsy or axillary lymph node dissection (ALND); and, 3) had a pre-surgical L-Dex measurement as well as at least 2 post-surgical measurements with the first post-surgical measurement within 180 days of surgery. Post-mastectomy reconstruction was allowed with either tissue expander/implant or autologous reconstruction; information on reconstruction techniques utilized was not available. Systemic therapy including chemotherapy and hormonal therapy was allowed and could be delivered as neo-adjuvant or adjuvant treatment. Exclusion criteria included implantable electronic devices (i.e., pacemakers), bilateral disease, pregnancy, renal failure, and heart failure.

Data collected included patient characteristics (age, height, weight, and menopausal status), treatment characteristics (operation type, SLN or ALND, number of nodes removed, and radiation therapy), L-Dex scores at each measurement point, and BCRL treatment. The L-Dex U400 is a bioelectrical impedance spectroscopy device that measures impedance ratios and displays these ratios as an L-Dex score. It should be noted that the L-Dex score is a derived value and is a linearly scaled derivation of the lymphedema index ratio (LIR), and can be used interchangeably (10). The baseline L-Dex score can be a positive or negative score with an increase in extracellular fluid

reflected in an overall increase in the L-Dex score. The testing was conducted utilizing a standardized measurement protocol (11). All patients underwent measurements in the supine position on a non-metallic table. Skin was prepped with alcohol and electrodes were placed on the midline dorsal surface of the wrist at the level of the ulnar styloid process and on the skin on the midline anterior surface of the ankle at the level of the medial and lateral malleolus bones.

A subset of patients underwent treatment for BCRL based on physician assessment of the patient, L-Dex scores, and clinical symptoms. No attempt was made to utilize specific cut-offs for L-Dex score or other metrics (e.g., arm circumference) to initiate BCRL treatment. As such, not every patient with an elevated L-Dex score post loco-regional treatment underwent BCRL treatment.

Statistical Analyses

Descriptive statistics (mean, median, standard deviation, minimum, and maximum for continuous variables, and number and percentage of subjects for categorical variables) were calculated for patient and surgical characteristics, and for absolute and changes in L-Dex values. Comparisons between patients who underwent lymphedema treatment (BCRL intervention subgroups) and those who did not have lymphedema treatment (no intervention subgroups) were made via 2-sample t-test for continuous variables, and Fisher's exact tests for categorical variables.

RESULTS

Patient characteristics for the entire cohort and by intervention sub-group status are presented in *Table 1*. The mean age for the entire group was 54 years old with 38% of patients treated with breast conserving therapy. Fifty four percent of patients underwent SLN biopsy with a mean of 7.9 nodes removed for all patients. The mean change in L-Dex score from baseline (prior to surgery or any other loco-regional treatment) to the first post-surgical L-Dex score measurement was 3.3 +/- 6.8.

Analysis of Patients Who Underwent BCRL Treatment

When comparing those patients that underwent BCRL treatment (n=13) to those that did not (n=37), no differences in age (p=0.71), height (p=0.62), weight (p=0.52), BMI (p=0.36), axillary surgery type (p=0.22), number of nodes removed (p=0.25), or frequency of radiation therapy (p=0.11) were noted (*Table 1*). There was a statistically significant higher rate of lumpectomies in the intervention group (61.5% v. 29.7%, p=0.05). As expected, patients referred for interventional lymphedema treatment by their physician had a statistically significant higher increase in L-Dex scores from baseline to the first post-surgical measurement than those patients who did not undergo intervention (8.1 v. 1.6, p=0.002). When evaluating all patients (n=50), there was a statistically significant reduction in L-Dex score from the first post-treatment measurement to the last post-treatment L-Dex measurement when comparing those that underwent intervention (n=13) to those that did not (n=37) (-4.3 +/- 5.5 v. 0.1 +/- 4.25, p=0.005, *Table 3*).

Analysis of Patients with Elevated L-Dex Scores after Operation

When evaluating characteristics for the subset of patients that had an elevated L-Dex score following operation (*Table 2*), no statistically significant differences were noted between those receiving BCRL treatment and those observed in the key variables of age (p=0.72), height (p=0.57), weight (p=0.06), BMI (p=0.10), axillary surgery type (p=0.47), number of nodes removed (p=0.81), and frequency of radiation therapy (p=0.14). A statistically significant increased L-Dex score from baseline to the 1st post-surgical

TABLE 1
Patient Characteristics

		Total (N=50)	With Intervention (N=13)	Without Intervention (N=37)	p-value
Age (yrs)	Mean +/- SD	54.0 +/- 12.6	52.9 +/- 9.8	54.4 +/- 13.5	0.71
	Range	29.9-81.6	35.8-63.4	29.9-81.6	
< 50	N (%)	22 (44.0)	6 (46.2)	16 (43.2)	
>= 50	N (%)	28 (56.0)	7 (53.8)	21 (56.8)	
Height (cm)	Mean +/- SD	163.6 +/- 7.5	162.6 +/- 6.5	163.8 +/- 7.9	0.62
	Range	149.9-177.8	149.9-170.2	149.9-177.8	
Weight (kg)	Mean +/- SD	73.2 +/- 17.8	75.9 +/- 17.2	72.2 +/- 18.1	0.52
	Range	49.9-142.9	52.2-115.2	49.9-142.9	
BMI (kg/m^2)	Mean +/- SD	27.5 +/- 7.0	29.0 +/- 7.9	26.9 +/- 6.7	0.36
	Range	19.8-52.4	20.6-45.0	19.8-52.4	
<25	N (%)	19 (38.0)	5 (38.5)	14 (37.8)	
25- < 30	N (%)	23 (46.0)	4 (30.8)	19 (51.4)	
>=30	N (%)	8 (16.0)	4 (30.8)	4 (10.8)	
Surgery					
Lumpectomy	N (%)	19 (38.0)	8 (61.5)	11 (29.7)	0.05
Mastectomy	N (%)	31 (62.0)	5 (38.5)	26 (70.3)	
Re-Excision Axillary Procedure	N (%)	4 (8.0)	2 (15.4)	2 (5.4)	0.27
Sentinel Node(s) Only	N (%)	27 (54.0)	5 (38.5)	22 (59.5)	0.22
Axillary Excision	N (%)	23 (46.0)	8 (61.5)	15 (40.5)	
Number of Nodes	Mean +/- SD	7.9 +/- 7.2	9.8 +/- 7.7	7.2 +/- 7.0	0.25
	Range	1.0-27.0	2.0- 23.0	1.0-27.0	
0-3	N (%)	20 (40.0)	5 (38.5)	15 (40.5)	
4-6	N (%)	10 (20.0)	1 (7.7)	9 (24.3)	
7-10	N (%)	7 (14.0)	2 (15.4)	5 (13.5)	
>=10	N (%)	13 (26.0)	5 (38.5)	8 (21.6)	
Radiation					
Yes	N (%)	28 (56.0)	10 (76.9)	18 (48.6)	0.11
No	N (%)	22 (44.0)	3 (23.1)	19 (51.4)	
Change in LDEX (Baseline to 1st Post-Surgery)	Mean +/- SD	3.3 +/- 6.8	8.1 +/- 7.3	1.6 +/- 5.8	0.002
	Range	(-7.8-20.2)	(-3.7-20.2)	(-7.8-16.9)	

measurement (10.1 v. 5.0, p=0.02) was noted. There was a statistically significantly greater reduction in L-Dex score from the first post-treatment measurement to the last post treatment L-Dex measurement when comparing those that underwent intervention (n=11) to those that did not (n=21) (-5.8 +/- 4.5 v. 0.1 +/- 4.2, p=0.001, *Table 4*).

TABLE 2
Patient Characteristics For Patients With Elevated Post-Surgical L-Dex Score

		Total (N=33)	With Intervention (N=11)	Without Intervention (N=21)	p-value
Age (yrs)	Mean +/- SD	54.5 +/- 13.2	53.3 +/- 9.9	55.1 +/- 14.8	0.72
	Range	29.9-81.6	35.8-63.4	29.9-81.6	
< 50	N (%)	13 (40.6)	5 (45.5)	8 (38.1)	
>= 50	N (%)	19 (59.4)	6 (54.5)	13 (61.9)	
Height (cm)	Mean +/- SD	162.8 +/- 7.1	161.8 +/- 6.6	163.3 +/- 7.4	0.57
	Range	149.9-177.8	149.9-170.2	152.4-177.8	
Weight (kg)	Mean +/- SD	70.7 +/- 14.7	77.4 +/- 18.5	67.1 +/- 11.3	0.06
	Range	49.9-115.2	52.2-115.2	49.9-86.2	
BMI (kg/m^2)	Mean +/- SD	26.7+/- 5.9	29.8 +/- 8.4	25.1+/- 3.4	0.10
	Range	19.8-45.0	20.6-45.0	19.8-28.9	
<25	N (%)	13 (40.6)	4 (36.4)	9 (42.9)	
25- < 30	N (%)	15 (46.9)	3 (27.3)	12 (57.1)	
>=30	N (%)	4 (12.5)	4 (36.4)	0 (0.0)	
Surgery					
Lumpectomy	N (%)	12 (37.5)	7 (63.6)	5 (23.8)	0.06
Mastectomy	N (%)	20 (62.5)	4 (36.4)	16 (76.2)	
Re-Excision Axillary Procedure	N (%)	3 (9.4)	2 (18.2)	1 (4.8)	0.27
Sentinel Node(s) Only	N (%)	15 (46.9)	4 (36.4)	11 (52.4)	0.47
Axillary Excision	N (%)	17 (53.1)	7 (63.6)	10 (47.6)	
Number of Nodes	Mean +/- SD	9.3 +/- 7.8	9.7 +/- 7.8	9.0+/- 8.0	0.81
	Range	1.0-27.0	2.0- 23.0	1.0-27.0	
0-3	N (%)	11 (34.4)	4 (36.4)	7 (33.3)	
4-6	N (%)	6 (18.8)	1 (9.1)	5 (23.8)	
7-10	N (%)	4 (12.5)	2 (18.2)	2 (9.5)	
>=10	N (%)	11 (34.4)	4 (36.4)	7 (33.3)	
Radiation					
Yes	N (%)	20 (62.5)	9 (81.8)	11 (52.4)	0.14
No	N (%)	12 (37.5)	2 (18.2)	10 (47.6)	
Change in LDEX (Baseline to 1st Post-Surgery)	Mean +/- SD	6.8 +/- 5.9	10.1 +/- 6.0	5.0 +/- 5.2	0.02
	Range	(0.2-20.2)	(2.3-20.2)	(0.2-16.9)	

DISCUSSION

The results of this analysis confirm that BIS can detect increases in L-Dex scores (reflecting extracellular fluid accumulation) early after breast surgery and that it can also detect reductions in L-Dex scores subsequent to treatment intervention for early onset

TABLE 3
Change in L-Dex Score With and Without BCRL Intervention

Statistic	With Intervention (N=13)	Without Intervention (N=37)	p-value
Mean	-4.3	0.1	0.005
Median	-4.5	0.1	
Std Dev	5.5	4.3	
Range	-13.0-4.9	-7.4- 7.3	

TABLE 4
Change in L-Dex Score With and Without BCRL Intervention for Those Patients With Elevated Post-Surgical L-Dex Score

Statistic	With Intervention (N=11)	Without Intervention (N=21)	p-value
Mean	-5.8	0.1	0.001
Median	-4.9	0.2	
Std Dev	4.5	4.2	
Range	-13.0-0.3	-7.4-7.3	

lymphedema. Further, when examining those patients with elevated L-Dex scores following surgery (potentially signaling the development of BCRL), interventional lymphedema treatment was associated with a significant reduction in the L-Dex score compared with no intervention. These results demonstrate that BIS has significant clinical utility as it can be used to monitor patients with early BCRL who undergo intervention and to follow these patients (through serial measurements) to document their short and long-term response to these treatments. These findings are consistent with previous data from Vanderbilt University which utilized BIS to monitor treatment response to BCRL (12). Prior to widespread clinical implementation, however, further studies are recommended to validate these findings on a larger scale and to compare these results to concurrent clinical measurements.

The findings of this analysis also support previous studies which document (1) that BIS is feasible to implement in the community oncology setting, (2) that BIS provides values that are surrogates for BCRL, and (3) that sub-clinical BCRL can be detected within 6 months of loco-regional treatment with BIS (11,13). Perometry represents an alternative modality for detecting BCRL with previous studies reporting that perometry and BIS provide comparable sensitivity for assessment of upper extremity lymphedema (14); however, perometry has significantly higher costs and space requirements making it more difficult to utilize routinely in community oncology settings.

Early Intervention for BCRL

Our findings are reinforced by increasing data that clearly support early intervention

for BCRL in order to prevent its irreversible sequelae when diagnosed at a later stage. For example, a phase III trial from Spain randomized 120 women who underwent ALND to manual lymphatic drainage, massage, exercise, and BCRL education or BCRL education only. This trial found that at one year, patients in the early intervention arm experienced significantly reduced rates of BCRL (7% v. 25%, p=0.01) (5). An Australian phase III trial of 65 women who underwent ALND randomized patients to prospective physiotherapy or surveillance and found that early treatment reduced the rate of chronic BCRL (11% v. 30%) (6). Also, a prospective study from Stout-Gergich et al evaluated patients with perometry to identify patients with early BCRL; patients identified underwent treatment with a compression garment and gauntlet which reduced arm volumes and limited further treatment (4). These findings are also consistent with a prospective study from the Mayo Clinic, which found that in patients with low volume BCRL (0-9% increase) at 6 months, 22% of patients progressed by 12 months with patients having persistent quality of life issues due to the BCRL (15).

Table 5 presents a summary of studies that have evaluated the impact of early intervention for BCRL. It should be noted that these studies were limited by their ability to evaluate sub-clinical arm volumes and the use of older diagnostic modalities (16-18). As previously noted, studies have documented that BIS has increased sensitivity compared to traditional BCRL diagnostic modalities and therefore can be used for the early detection of BCRL. These published findings with the data from the present analysis, support the use of BIS for early detection and subsequent BIS follow-up after intervention.

Prospective trials utilizing BIS are underway to evaluate the feasibility and outcomes associated with early detection and intervention. For example, in a trial from Bryn Mawr Hospital, patients undergo pre-operative assessment with both BIS and water displacement and subsequently will undergo serial measurements. If a patient has an L-Dex score greater than 10 or is outside the normal range, they will be randomized to a compression sleeve or observation (19). Also, a trial at Stanford University is prospectively enrolling patients to undergo serial BIS measurements with patients diagnosed with BCRL randomized to interventions to prevent progression (20).

Study Limitations

Although our findings are consistent with previous bioimpedance studies (using single frequency, multi-frequency or BIS) that have documented the increased sensitivity of bioimpedance, and the ability of the technique to be utilized in the clinic, there are limitations to this analysis (11,13). While the data for this manuscript were collected prospectively, this was a retrospective review and is subject to the limitations and biases of such an analysis. It is also important to note that our cohort was small (n=50) and our subset analysis even smaller (n=32), limiting the ability of the study to make more definitive conclusions. Our report is also limited by its lack of long term follow-up and long term L-Dex scores. Finally, although measurements were made before and after intervention, no standardized time points for measurement were utilized, and no documentation of the concurrent clinical findings was available for comparison. However, despite these limitations, this study demonstrates that BIS can be used to identify and monitor BCRL following treatment. When combining this with BIS's ability to detect sub-clinical BCRL, it stands to reason that future protocols examining early detection and intervention could employ BIS as a diagnostic and subsequent follow up assessment modality. Ultimately, it is likely that BIS could also be used to identify and stratify patients based upon their potential risk for developing BCRL.

TABLE 5
Review of Studies Addressing Early Detection and Intervention for Breast Cancer Related Lymphedema

Institution	Type	Number of Patients	Randomization	Key Findings
Alcala de Heneres University[5]	Prospective/ Randomized	120	Early manual lymphatic drainage, massage, exercise v. education only	Early physiotherapy group had a reduced rate of lymphedema (7% v. 25%, p=0.01) at one year
University of Queensland[6]	Prospective/ Randomized	65	Physiotherapy v. surveillance	Decreased rates of lymphedema with physiotherapy 11% v. 30%) at two years
National Naval Medical Center[4]	Prospective/ Non-Randomized	43	Prospective surveillance program with compression garment use	After use of compression sleeve, 48 cc decrease in arm volume (p<0.001)
University of Pennsylvania[16]	Retrospective	1,713	--	At 1 year, 80% freedom from progressive lymphedema for mild (0.5-2.0 cm) lymphedema at presentation; at five years, 67% freedom from progression at five years
University of New Mexico[17]	Retrospective	69	--	78% reduction in arm volume with <250 cc edema at diagnosis v. 56% 250-500 cc, and 38% >500 cc
Lund University, Sweden[18]	Retrospective	292	--	16% v. 10% progression to chronic lymphedema for large volume (>20% increase) at diagnosis compared to small volume (5-10% increase) at diagnosis

CONCLUSIONS

BIS detected increases in L-Dex scores early after breast surgery and reductions in L-Dex scores as a response to lymphedema treatment. These results demonstrate that BIS conducted in breast cancer clinical settings can be utilized to objectively identify early onset lymphedema and to aid clinicians in monitoring the efficacy of therapeutic intervention in patients treated for BCRL. Further prospective studies are underway to validate these findings.

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