Retrospective Review

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Modulate the Function of Myelinated Fibers after Chemotherapy: A Quantitative Sensory Testing Study

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Background: Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have sufficient scientific support for their use as tissue protectors. Preliminary studies suggest that their angiotensin-II type 2 receptor (AT2R)-blocking properties have a beneficial profile in the treatment of neuropathic pain.

Objectives: The purpose of the current study was to quantify the extent of the somatosensory effects of ACEI and ARB in cancer patients with chemotherapy-induced peripheral neuropathy.

Study Design: We performed a retrospective review of cancer patients with peripheral neuropathy of the upper limbs induced by known neurotoxic anti-cancer agents.

Setting: Pain Medicine department at academic tertiary care cancer center.

Methods: Using our quantitative sensory testing (QST) data bank, we retrospectively compared the tactile function and the touch, sharp, and thermal thresholds of patients who were previously receiving ACEI or ARB for high blood pressure with these variables in controls who were not receiving ACEI or ARB.

Results: Of the 209 patients available for analysis, 145 met inclusion criteria. Baseline characteristics of patients included were generally similar. We identified 29 patients who were receiving AT2R inhibitors prior to starting chemotherapy. Touch thresholds were statistically lower in the thenar aspect of hand in the study group (patients who received AT2R inhibitors) than in the control group [mean (± SD), median 3.03 g (± 11.05), median 0.56 g and 6.75 g (± 18.28), 0.56 g, respectively ($P = 0.0441$)]. Similarly, the cold pain threshold was statistically higher at the thenar area for the study group [mean (± SD), median 13.23°C (± 8.02), 11.73°C] than for controls [9.89°C (± 6.62), 10.05°C ($P = 0.0369$)].

Limitations: Inadequacies in the original data acquisition and documentation of the QST and the medical records could not be addressed due to the retrospective nature of the study. Similarly, a discrepancy on the size of the comparison groups could not be reconciled. In addition, based on the available information and the lack of documented concomitant pain levels, we did not find an objective parameter able to correlate the QST findings with pain levels.

Conclusions: AT2R inhibitors might offer partial and selective neuroprotective qualities of the myelinated fibers A-β and A-δ in cancer patients who receive neurotoxic chemotherapy.

Key words: Quantitative sensory testing, chemotherapy-induced peripheral neuropathy, angiotensin-II type 2 receptor (AT2R)

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Among cancer patients, pain is one of the most problematic symptoms, one that can persist even after cure or remission. More than 20% of cancer patients have pain related to chemotherapy, radiation therapy, or surgery (1). Chemotherapy-induced peripheral neuropathy (CIPN) is a particularly vexing problem, with an overall incidence of approximately 38% in patients treated with neurotoxic agents (2). In the absence of effective treatment, dose reductions or "treatment holidays" are common strategies used during the onset of neuropathy, but such strategies may reduce the clinical effectiveness of cancer treatment. Furthermore, 5% to 15% of patients with CIPN develop refractory pain that often requires costly and invasive treatments such as spinal cord stimulators or intrathecal drug delivery systems (3,4). With limited pharmacological options to treat these patients, various possibilities are being explored. While some research targets development of new agents, other researchers are exploring the analgesic properties of various drugs currently used to treat non-pain–related conditions. Among these latter drugs, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are gaining special attention. These commonly used antihypertensive drugs have also been used extensively for their tissue-protection properties (5-9). The tissue-protection qualities of these agents are based on their ability to inhibit the angiotensin-II type 1 receptor (AT1R). AT1R are associated with vasoconstriction, inflammation, water and salt retention, and vascular remodeling (10). In contrast, the function and role of the angiotensin-II type 2 receptor (AT2R) remain to be elucidated. Bali et al (11) suggested that ACEI and ARB, via their AT2R effects in the brain, might have a beneficial profile in the treatment of neuropathic pain by inducing release of endogenous opioids. AT2R inhibitors have been associated with a reduction of pain signaling through their expression in small- to medium-sized cultured neurons of humans and rats and their dose-related functional inhibition of capsaicin responses (12). In addition, a study on rats showed that hydralazine and captopril diminished responsiveness to noxious stimuli via opiate receptors within the central nervous system and that pain perception changes appeared to be unrelated to the blood pressure regulation (13) when delivered before and after the development of diabetes. Similarly, significant reductions of hyperalgesic behavior using the hot plate and electric footshock thresholds have been reported in hypertensive animals treated with ACEI (14). More recently, a double-blind, randomized, phase 2 clinical trial of an AT2R-specific inhibitor (EMA 401) in patients with post-herpetic neuralgia demonstrated superior pain relief compared with placebo at the end of 28 days of treatment (15).

In the current study, we used (to our knowledge, for the first time) quantitative sensory testing (QST) to assess the role of AT2R inhibitors in preventing the development of CIPN. QST, a non-invasive method that assesses sensory and pain perception, can objectively evaluate the function and integrity of both large and small fibers of the peripheral nerves (16,17). We hypothesized that treatment with ACEI or ARB would protect patients from the development of neuropathy following neurotoxic chemotherapy. In order to estimate the effectiveness of these drugs, we performed a retrospective cohort study of previously prospectively collected QST data for patients at The University of Texas MD Anderson Cancer Center who underwent cancer treatment and had clinical evidence of CIPN. We extracted the QST values for patients taking ACEI/ARB prior to neurotoxic drug exposure and we compared their values to those of controls who did not receive ACEI or ARB.

Methods

Study Setting and Population

For the past 12 years, an open protocol has collected longitudinal QST data from patients with active cancer receiving treatment with chemotherapy. Data on QST values in a group of non-cancer asymptomatic volunteers was also created to be used as reference. This database also contains demographic information and data regarding comorbid diseases and current cancer treatment. This protocol was reviewed and approved by the institutional review board (IRB protocol # ANS 00-339). Patient participation was voluntary, and informed consent was obtained before patients were enrolled in the study. Patient information was stored in a secure database, and access to the database for secondary projects such as the current report required a separate approval by the IRB, which was obtained.

Selection of Cases

Patients in the QST data bank were identified and invited to participate in the QST assessment after a routine screening process of patients registered for cancer treatment. Patients were under the care of different oncology subspecialties. No cancer, stage, or

chemotherapy agent was excluded. Recruitment procedures and QST protocols were described in their entirety to the patients. All patients invited to participate had given written informed consent prior to testing and were free to withdraw from the QST studies at any time. To participate, all patients had to be able to understand the QST study modalities and had to be able to consent, participate, and report the testing thresholds. No financial incentive was offered to participants.

Our study population consisted of a subgroup of individuals of the QST data bank. This subgroup of patients had been known by the Pain Medicine service who made the diagnosis of CIPN. All patients had clinical evidence of symmetrical compromise of the upper limbs. Of this group, we selected those who had undergone QST assessment at one month or more after starting the neurotoxic agents. We excluded patients who had discontinued ACEI/ARB therapy prior to the QST evaluation.

Quantitative Sensory Testing

QST testing was performed at the QST laboratory of MD Anderson Cancer Center. All sensory tests were performed at the index finger tip, thenar and dorsal aspect of hand, and the thenar aspect of proximal forearm. The QST battery consisted of the following 5 measurements.

Touch detection threshold.

Touch detection thresholds were determined using von Frey monofilaments in the up/down method (18). The fibers were applied perpendicularly to a skin area for approximately one second starting at a bending force of 0.05 g. If the patient failed to detect the stimulus, the next higher force monofilament was applied to the same skin location. When the patient was able to detect the stimulus, the next lower monofilament was applied. The filament detected 4 times was assigned as the touch detection threshold.

Bumps detection.

Bumps detection is a fine touch tool based on tactile detection of minute elevations on a smooth glass surface (19). Three separate etched plates, each one containing 12 squares (1.5 × 1.5 inch each) compose this kit. The squares have 5 flat circles of a different color. One of the circles of each square contains a bump of 550-µm diameter. On plate one, bumps vary from 2.5 to 8.0 µm in height; on plate two, bumps vary from 8.5 to 14.0 µm in height; and on plate three, bumps range from 14.5 to 26 µm in height. Patients are instructed to use the index finger to palpate the 5 circles within each square. They begin each session palpating bumps in plate 2. Unable to see the location of the bumps, patients report the color where they perceive the bump. If participants correctly identify the location of the bumps, they progress to plate one (2.5 to 8 µm). Patients unable to detect the bumps on plate 2 are tested with plate 3 (14.5 to 26 µm). The bumps detection threshold is determined to be the smallest bump correctly identified in sequence to the next 2 higher bumps. For this test, basic colors are used, and the individual is assumed to be able to see, distinguish, and name the colors used.

Sharpness detection threshold.

The sharpness detection threshold is determined with the use of a weighted needle device (20,21). A blunted 30-gauge needle (200 µm diameter) is engaged to a calibrated brass weight fitted into the Luer connection. The assembly is placed inside the cylinder of a 10-mL syringe so the weighted assembly moves freely within the syringe that the needle comes out of the tip. When the needle is applied to the skin, a consistent force is applied. The forces used are 8, 10, 16, 20, 32, 64, and 128 g. Each stimulus is applied for about one second, in ascending weight order. The patients are instructed to indicate whether the stimulus is perceived as touch, pressure, sharp, or pain. Each trial terminates with the report of sharp or pain sensation. The sharpness detection threshold is defined as the mean calculated of 3 trials randomly separated by 30 to 90 seconds.

Heat and cold detection thresholds.

The threshold for temperature (heat and cold) pain is determined using a computer controlled Peltier device in a Marstok method (22-24). A radiometer is used at the outset of testing to ascertain the baseline skin temperature at the body testing sites. Baseline temperature was set at 32°C (89.6 F), and the probe either gradually cooled at 0.50°C/s or heated at 0.3°C/s. Patients are instructed to signal when a change in temperature (cooler or warmer) is first detected and then when the stimulus is perceived as painful. No correction is made for reaction time delay. If a patient fails to perceive heat or cold pain before the cutoff temperature of 51.5 or 3°C held for 10 seconds, respectively, then this is recorded as the default value. The final threshold value is determined by averaging the results of 3 heat/cold ramp trials randomly separated by 30 to 90 seconds.

Statistical Analysis

Continuous variables and categorical variables were summarized using means ± standard deviations, medians, and counts (percentages), respectively. Patient demographics and QST results were compared between patients who had received ACE/ARB and patients who had not, utilizing 2-sample t-test or Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables. *P*-values of less than 0.05 indicated statistical significance. SAS version 9.4 (SAS Institute INC, Cary, NC) was used for data analysis.

Results

Study Groups

A total of 209 patient charts were reviewed, of which 64 did not meet inclusion criteria. Of those, 22 were volunteer non-cancer asymptomatic individuals used as controls (none of them was taking ACEI/ARB), 6 had been taking ACEI/ARB but had discontinued use prior to the QST due to medical complications, and 36 had inadequate medical records concerning medication usage, or had QST done only before starting chemotherapy (20 were taking ACEI/ARB). These latter gaps were important and precluded imputation of the data. The final study population therefore consisted of 145 patients. All had symptomatic peripheral neuropathy described as diverse painful sensory symptoms in a glove distribution. Twenty-nine patients had received ACE/ARB for essential hypertension prior to being established in our institution; 116 had not received ACE/ARB and hence were used as the control group (Fig. 1).

Demographics

Demographic information for the 145 patients included in the analysis is summarized in Table 1A and

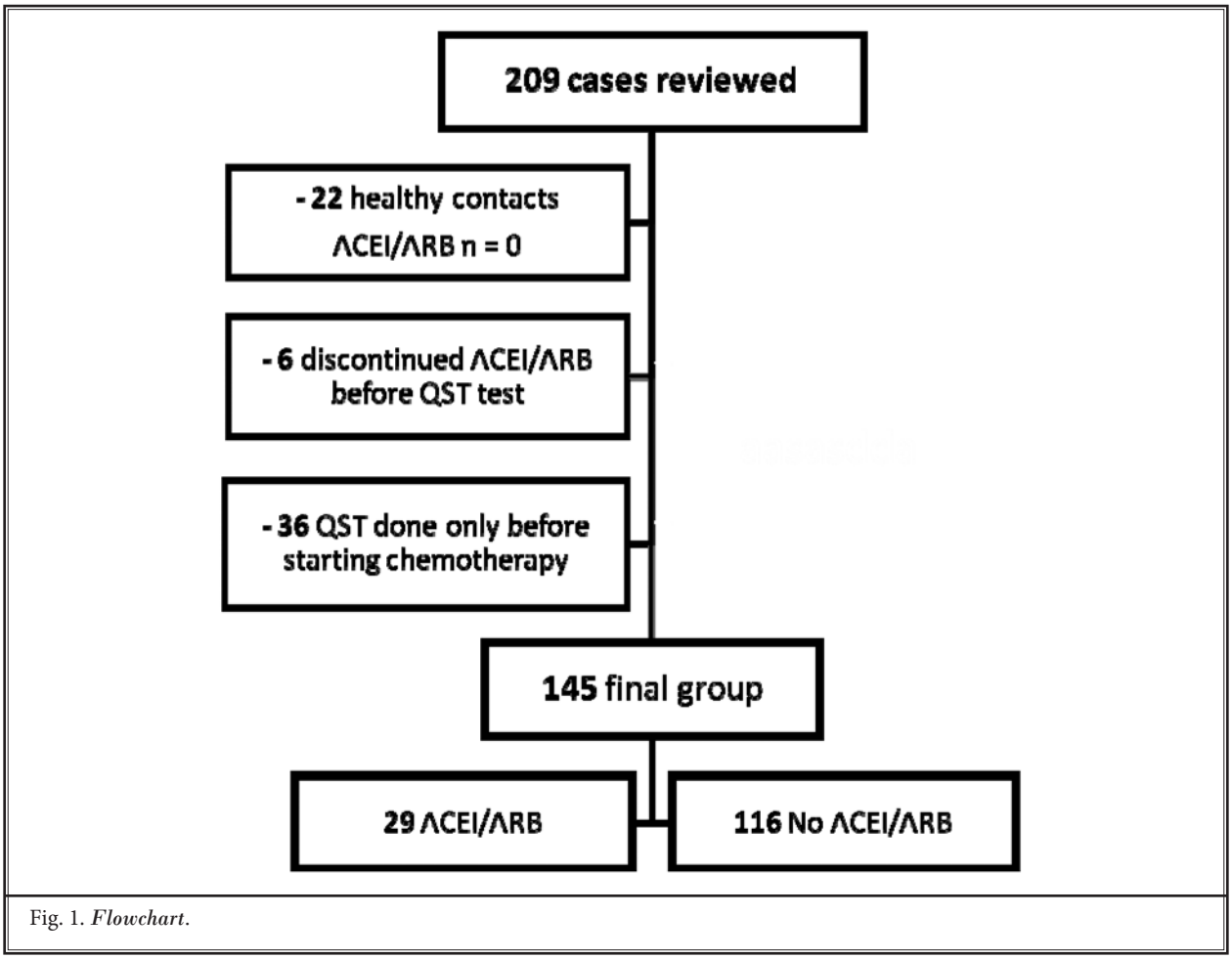

Fig. 1. *Flowchart.*

Table 1A. *Patient demographics.*

Covariate	Levels	ACE/ARB (N=29)	No (N = 116)	*P*-v
Age, years	Mean ± SD	62.62 ± 8.08	63.19 ± 12.05	0.8101
Ethnicity	Asian	0(0%)	1(0.9%)	0.1654
	Black	5(17.2%)	12(10.3%)	
	Hispanic	5(17.2%)	13(11.2%)	
	Other	1(3.4%)	0(0%)	
	White	18(62.1%)	90(77.6%)	
Gender	Female	12(41.4%)	55(47.4%)	0.5599
	Male	17(58.6%)	61(52.6%)	
Diagnosis	ALL	2(6.9%)	2(1.7%)	0.1991
	AML	0(0%)	1(0.9%)	
	APL	1(3.4%)	0(0%)	
	B-cellL	0(0%)	9(7.8%)	
	Breast	1(3.4%)	13(11.2%)	
	Cervix	0(0%)	1(0.9%)	
	Colon	1(3.4%)	2(1.7%)	
	Endometrial	0(0%)	1(0.9%)	
	Gastric	0(0%)	1(0.9%)	
	Liver	0(0%)	1(0.9%)	
	Lung	1(3.4%)	4(3.4%)	
	Lymph	0(0%)	6(5.2%)	
	MM	21(72.4%)	58(50%)	
	Mediastinum	0(0%)	1(0.9%)	
	Melanoma	0(0%)	1(0.9%)	
	Neck	0(0%)	1(0.9%)	
	Oral	0(0%)	2(1.7%)	
	Ovarian	0(0%)	2(1.7%)	
	Prostate	0(0%)	2(1.7%)	
	Renal	0(0%)	1(0.9%)	
	Sarcoma	0(0%)	4(3.4%)	
	T-cellL	1(3.4%)	0(0%)	
	Testicle	0(0%)	1(0.9%)	
	Thyroid	1(3.4%)	0(0%)	
	Tongue	0(0%)	2(1.7%)	

1B. Mean age was 63 years, with a range of 29 – 86 years. There were 67 women and 78 men. Most patients (74.5%) were Caucasian.

The most common diagnoses were multiple myeloma (79 patients, 54.5%), breast cancer (14, 9.7%), and non-Hodgkin's B-cell lymphoma (9, 6.2%). The rest of the patients had solid and liquid cancers of diverse etiologies.

None of the patients had a history of diabetes mellitus, alcoholism, or AIDS that might have contributed to the development of neuropathy. However, 8 patients

Table 1B. *Chemotherapy regimen with vs. without ACEI/ARB.*

Chemotherapy	ACEI/ARB	No ACEI/ARB	*P*-value
Bortezomib	20(69%)	51(44%)	.0160
Taxanes	2(6.9%)	25(21.6%)	.1068
Platins	1(3.4%)	20(17.2%)	.0761
Vinca	3(10.3%)	17(14.7%)	.7651
Thalidomide	4(13.8%)	14(12.1%)	.7589
Others	2(6.9%)	8(6.9%)	1.000

Table 2. *Comparison of QST results by ACEI/ARB intake.*

Covariate	ACEI/ARB (N = 29)	Control (N = 116)	*P*-value
Bump detection A (μm)	6.1 ± 3.68; 5.5	5.65 ± 3.2; 5.07	0.5071
Touch detection A (g)	4.33 ± 16.51; 0.56	9.4 ± 23.04; 0.56	0.0760
Touch detection B (g)	3.03 ± 11.05; 0.56	6.75 ± 18.28; 0.56 3.42)(0.15; 89.4)	0.0441
Touch detection C (g)	1.13 ± 1.24; 0.56	2.14 ± 6.2; 0.56	0.8664
Sharpness detection A (g) (grams)	48.55 ± 33.22; 42.7	38.69 ± 24.47; 36.67	0.0784
Sharpness detection B (g)	30.07 ± 24.16; 27.3	28.87 ± 20.36; 22	0.9130
Sharpness detection C (g)	21.26 ± 25.43; 12	20.44 ± 18.7; 10	0.8204
Warm detection A (°C)	40.3 ± 3.86; 40.07	40.52 ± 3.34; 39.9	0.7553
Warm detection B (°C)	38.59 ± 3.07; 38.3	38.89 ± 3.17; 38.27	0.6461
Warm detection C (°C)	39.18 ± 2.82; 39.2	38.87 ± 3.23; 38.3	0.6442
Heat pain A (°C)	47.16 ± 3.45; 47.93	47.85 ± 2.85; 48.03	0.2621
Heat pain B (°C)	44.72 ± 4.21; 45.35	45.5 ± 3.63; 45.65	0.3241
Heat pain C (°C)	45.16 ± 3.31; 46.03	45.32 ± 3.52; 45.9	0.8280
Cool detection A (°C)	22.96 ± 6.35; 24.5	23.31 ± 5.12; 23.7	0.8803
Cool detection B (°C)	26.11 ± 3.23; 27.02	24.39 ± 4.96; 25.4	0.0739
Cool detection C (°C)	25.68 ± 2.54; 25.57	24.55 ± 4.84; 25.8	0.7979
Cold pain A (°C)	7.83 ± 7.08; 3.83	6.8 ± 5.05; 3.46	0.7757
Cold pain B (°C)	13.23 ± 8.02; 11.73	9.89 ± 6.62; 10.05	0.0369
Cold pain C (°C)	10.97 ± 7.87; 6.97	9.56 ± 6.6; 8.63	0.2380

Values are presented as means ± SD; median. Abbreviations: A, index finger tip; B, thenar aspect of hand; C, flexor aspect of proximal forearm.

had elevated blood sugar associated with chemotherapy, so-called chemo-diabetes. At the QST assessment, all patients had peripheral neuropathy of the upper limbs that was presumably induced by chemotherapy with known neurotoxic agents. The most common cancer therapeutics used were bortezomib (n = 71 patients, 49%), taxanes (27, 18.6%), platins (21, 14.5%), and vinca alkaloids (20, 13.8%).

QST Results

Clinical characteristics and QST values are summarized in Table 2 for patients who were taking ACE/ARB and for controls who were not.

Touch detection thresholds.

The values were obtained in areas reported as having sensory disturbance. Touch detection threshold, a gauge of A-β fiber function, most especially Merkel disc function (25,26), was statistically lower on the thenar aspect in the patients who had long-standing therapy with ACEI/ARB than in controls [mean (± SD), median of 3.03 g (± 11.05), 0.56 g compared with 6.75 g (± 18.28), 0.56 g; *P* = 0.0441] (Fig. 2). In this QST laboratory, reference volunteers have reported mean (± SD) values for touch detection thresholds of 0.26 g (± 0.03) at the thenar site. At the index tip, the results followed a similar trend [4.33 g (± 16.51), 0.56 g compared with 9.4 g (± 23.04), 0.56 g; *P* = 0.0760] (Fig. 3). The touch detection thresholds in the forearm did not differ significantly between the groups.

Overall, the touch detection threshold in the sensory compromised area of patients in the ACEI/ARB group was lower in the thenar area than in controls not taking those medications (Figs. 2 and 3).

Bumps detection.

Similar to the touch detection threshold, the Bumps detection test has been used to measure the A-β fiber function (27), most closely reflecting Meissner's corpuscle function. The data for Bumps detection are shown in Table 2. Patients in the 2 groups did not differ significantly at the index fingertip, the only area tested

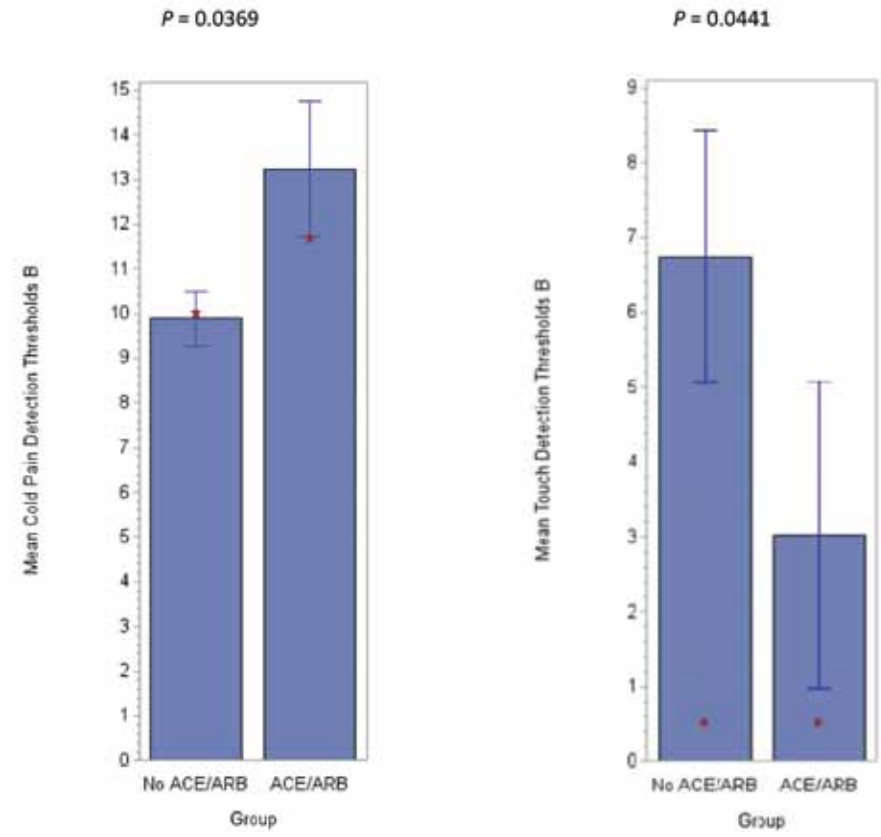

Fig. 2. *Cold pain detection and touch detection thresholds—Thenar aspect. Bar graphs on the left side of the figure show the mean (blue bar) ± standard error (blue line) along with the median (red asterisk) of the cold pain detection threshold (in degrees Celsius) at the thenar aspect of the hand in the control group (no ACEI/ARB) and the study group. The bar graphs on the right side compare the means for the touch detection threshold (bending force in grams) at the thenar aspect of the hand between the groups. The skin test sites show a statistical difference between the groups favoring the ACEI/ARB group ($P < 0.05$).*

[mean (± SD), median were 6.1 µm (± 3.68), 5.5 µm in the study group and 5.65 µm (± 3.2), 5.07 µm in the control group].

Sharpness detection threshold.

The data for sharpness perception, largely mediated by A-δ fibers, are shown in Table 2. Group comparison showed a trend for an increase in the sharpness detection threshold within the pain area at the fingertips in the study group [mean (± SD), median of 48.55 g (± 33.22), 42.7 g] compared with the controls [38.69 g (± 24.47), 36.67 g] ($P = 0.0784$) (Fig. 3). The mean (± SD) sharpness detection threshold at the fingertips in the volunteer controls in this QST laboratory has been reported as 24.6 g (± 2.9).

Heat and cold detection thresholds.

The cool detection threshold and cold-induced pain are both functions of the A-δ fiber. Our most important finding was the statistical difference in cold-induced pain at the thenar site [mean (± SD), median of 13.23°C (± 8.02), 11.73°C in the ACEI/ARB group and 9.89°C (± 6.62), 10.05°C in the control group ($P = 0.0369$)] (Fig. 2). The cool detection threshold in the volar site had a similar trend, with values of 26.11°C (± 3.23), 27.02°C for the study group and 24.39°C (± 4.96), 25.4°C for the controls ($P = 0.0739$) (Table 2, Fig. 3). At the volar aspect and forearm sites no significant differences between the groups were found.

The warmth detection threshold and heat-induced pain are both functions of the C fiber (19). Our study

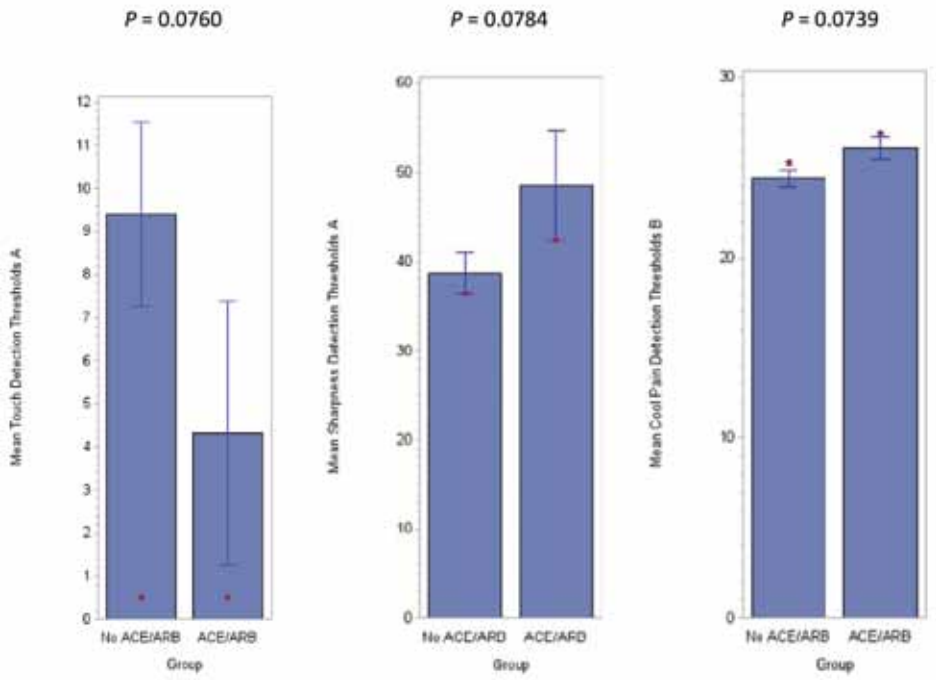

Fig. 3. *Touch & sharp threshold at fingertips; cool detection at volar aspect. Bar graphs on the left side of the figure show the mean (blue bar) ± standard error (blue line) along with the median (red asterisk) of the touch detection threshold (bending force in grams) at the finger tips for the control group (no ACEI/ARB) and the study group. Bar graphs in the middle show the mean for the sharpness detection threshold (in grams of weight applied) at the fingertip between the same groups. Bar graphs on the right side compare the mean of the cool detection threshold temperature (in degrees Celsius) at the thenar aspect of the hand between the groups. The skin test sites show a difference between the group of subjets in favor of the ACEI/ARB, but there was no statistical difference (P > 0.05).*

showed no significant difference between the groups at all body sites tested (Table 2).

Treatment Intervention

The ACEI and ARB medications included both generic and proprietary brands, with all medications for oral consumption. The doses and daily schedule varied from case to case. Overall well-controlled blood pressure is clinically indicated in order to receive most chemotherapy agents. This was used as a surrogate marker for compliance.

When the ACEI and ARB groups were compared individually with the control population, the differences in QST values were not statistically significant (Table 3). However, the ARB group had a more favorable profile than the ACEI. Values for the touch detection threshold at the thenar aspect [mean (± SD), median] were 1.32 g (± 1.97), 0.56 g in the ARB group and 4.42 g (± 14.84), 0.56 g in the ACEI, compared with 6.75 g (± 18.28), 0.56 g in the control group. Similarly, values for the cold pain threshold at the thenar aspect were 14.56 °C (± 8.15), 15.28°C in the ARB group and 12.23°C (± 8.04), 10.9°C in the ACEI group compared with 9.89°C (± 6.62), 10.05°C in the control group (Table 3).

Discussion

Our study retrospectively examined the sensory changes in cancer patients who were taking ACEI or ARB and developed CIPN. We found several differences in the QST values, suggesting a neuro-modulating effect of ACEI/ARB over certain fibers. The touch thresholds were lower at the thenar site and had a similar trend at the fingertips. Values for cold-induced pain and cool sensation threshold were both higher at the thenar site, and the sharp detection threshold showed a trend to be higher at the finger tips. However, the bump detection and the heat thresholds showed no difference between the groups. Overall, the values observed sug-

Table 3. *Comparison of QST Results by ACEI intake and ARB Intake separately.*

Covariate	ACE (N = 16)	ARB (N = 13)	Control (N = 116)	*P*-value
Bump detection (μm)	6.18 ± 3.59; 5.7	6.01 ± 3.93; 5.08	5.65 ± 3.2; 5.07	0.8752
Touch detection A (g)	6.37 ± 22.17; 0.36	1.82 ± 2.97; 0.56	9.4 ± 23.04; 0.56	0.1929
Touch detection B (g)	4.42 ± 14.84; 0.56	1.32 ± 1.97; 0.56	6.75 ± 18.28; 0.56	0.1311
Touch detection C (g)	1.23 ± 1.33; 0.56	1 ± 1.17; 0.56	2.14 ± 6.2; 0.56	0.6351
Sharpness detection A (g)	43.96 ± 30.23; 41.35	54.21 ± 37.01; 44.7	38.69 ± 24.47; 36.67	0.1751
Sharpness detection B (g)	24.42 ± 14.72; 22	37.02 ± 31.56; 32	28.87 ± 20.36; 22	0.5031
Sharpness detection C (g)	16.96 ± 15.28; 10.33	26.56 ± 34.08; 12.7	20.44 ± 18.7; 10	0.6088
Warm detection A (°C)	40.86 ± 4.59; 39.74	39.6 ± 2.73; 40.17	40.52 ± 3.34; 39.9	0.9123
Warm detection B (°C)	38.98 ± 3.61; 38.43	38.11 ± 2.29; 37.67	38.89 ± 3.17; 38.27	0.7311
Warm detection C (°C)	39.24 ± 2.86; 39.35	39.1 ± 2.89; 38.97	38.87 ± 3.23; 38.3	0.8181
Heat pain A (°C)	47.6 ± 3.74; 48.53	46.61 ± 3.13; 46.7	47.85 ± 2.85; 48.03	0.3428
Heat pain B (°C)	45.12 ± 4.78; 45.86	44.24 ± 3.51; 45.3	45.5 ± 3.63; 45.65	0.5882
Heat pain C (°C)	45.48 ± 3.32; 46.28	44.77 ± 3.38; 46.03	45.32 ± 3.52; 45.9	0.8415
Cool detection A (°C)	21.86 ± 7.21; 23.05	24.33 ± 5.04; 25.73	23.31 ± 5.12; 23.7	0.5649
Cool detection B (°C)	26.13 ± 3.6; 27.27	26.08 ± 2.83; 26.85	24.39 ± 4.96; 25.4	0.1888
Cool detection C (°C)	25.56 ± 2.72; 26.02	25.82 ± 2.41; 25.3	24.55 ± 4.84; 25.8	0.9607
Cold pain A (°C)	6.16 ± 5.62; 3.03	9.88 ± 8.32; 5.43	6.8 ± 5.05; 3.46	0.1957
Cold pain B (°C)	12.23 ± 8.04; 10.9	14.56 ± 8.15; 15.28	9.89 ± 6.62; 10.05	0.0909
Cold pain C (°C)	10.66 ± 8.11; 6.38	11.35 ± 7.88; 7.93	9.56 ± 6.6; 8.63	0.4401

Values are presented as means ± SD; median. Abbreviations: A, index finger tip; B, thenar aspect of hand; C, flexor aspect of proximal forearm.

gest that ACE/ARB offer a protective effect over fibers A-β and A-δ, both of which are known to be myelinated (28). However, with the fact that 19 comparisons (bump detection A, touch detection A, etc.) were made on the same patients and *P*-values associated with touch detection threshold and cold-induced pain at the thenar site were 0.0441 and 0.0369, further study with a larger sample size is warranted to confirm our findings after adjusting for multiple comparisons.

Notably, the benefits found were limited to the glabrous skin, with no effect for hairy skin. This area of myelinated nerve fiber protection correlates with the area of maximal symptoms described in patients affected by chemotherapy agents such as Bortezomib (29), and such protection could be a therapeutic development in cancer patients.

For years, the effects on pain of ACEI and ARB agents have been the subject of controversial reviews, with some authors suggesting that such medications have a beneficial profile (30-32) and other authors describing the opposite (33,34). With a better understanding of the pain mechanisms, significant progress has been made. By understanding the function and mechanisms of small fibers in neuropathic pain, and the effect of the ACEI/ARB on these fibers, the knowledge gap regarding the analgesic effect should narrow. The AT2R inhibition properties of ACEI/ARB and the effect on certain myelinated fibers point to an answer.

The vasoconstriction, aldosterone and vasopressin release, sodium and water retention, and sympathetic facilitation caused by angiotensin-II are mediated by AT1R (35). Although it is known that ACEI are inhibitors of angiotensin-II synthesis and that ARB are AT1R blockers, we do not know with certainty what effect and how significant an effect ACEI and ARB might have on AT2R. Still, in our study, independent tabulation of both agents suggests that ARB might have a more favorable profile on the protection of myelinated fibers. Interestingly, recent investigations have established a role for the AT2R in the modulation of various biological processes, including tissue repair and apoptosis (36).

Preclinical studies in cultured human and rat dorsal root ganglion cells demonstrated the expression of AT2R in sensory neurons and suggested that those

receptors could play a role in nociception and neuronal regeneration (37,38). This concept was later proven in animal models with neuropathic pain (39,40). Additional studies on animal models with antiretroviral agent–induced neuropathy have supported similar beneficial effects of the AT2R antagonism (41). Remarkably, a recent randomized clinical trial using EMA401, a highly selective AT2R-blocking agent, was able to demonstrate clinical effectiveness of this agent in patients with post-herpetic neuropathy (15). Of note, EMA401 is still not commercially available for clinical use.

To date, the beneficial profile of the AT2R inhibition has been directly demonstrated only with the use of EMA401. Moreover, research studies of ART2 inhibitors have been designed to target indiscriminately neuropathies of any etiology. Thus, the random utilization of AT2R inhibitors in neuropathic pain treatment might generate general information before a clear understanding of the precise indication or patient profile is determined.

Perhaps somatosensory phenotyping may help narrow the search. Somatosensory phenotyping, a characterization of sensory abnormalities, is considered one of the most practical clinical applications of QST in the diagnosis of neuropathic pain (42). Through the application of precise stimuli of measurable controlled intensity, QST can estimate the function of small fibers of peripheral nerves. In clinical trials, QST has played an important role in the diagnosis and monitoring of peripheral nerve pathologies (16,17).

Our study used QST and suggested that ACEI/ARB are protective of the myelinated fibers (A-β and A-δ). Unfortunately, its retrospective design does not provide strong evidence of clinical implications. However, our findings provide the basis for future prospective studies of ACEI/ARB that can apply to cancer patients with CIPN. Among patients with cancer, treatment is frequently discontinued or requires treatment "holidays" due to the unresolved pain of peripheral neuropathies (43). QST studies have identified a profile of patients who can potentially benefit from such neuroprotective agents as AT2R inhibitors. Of these cancer patients, the prime beneficiaries might be those treated with vincristine, paclitaxel, and Bortezomib, all known to affect primarily the myelinated fibers (A-β and A-δ) (28,44,45). Other potential targets include patients with demyelinating neuropathies (46,47).

The encouraging clinical suggestions of the current study are limited by its retrospective nature. There is an unequal sample size of patients' groups. It also takes into account missing or incomplete data that is contingent on the quality and accuracy of provider documentation in the medical records. ACEI/ARB medications, their bran d, dose, and timing were documented. However, patient compliance in taking the medications was an assumption since a well-controlled blood pressure was required to be part of these cancer treatment protocols. In addition, the uniformity of symptoms described in all patients as of glove distribution sensory disturbance and the associated pain syndrome suggest a pattern that differs in magnitude alone. Furthermore, the basis for the etiology of chemotherapy-mediated nerve injury remains unknown (48), and therefore the association between chemotherapy agents and the development of symptoms documented in the medical records is direct but circumstantial. Finally, since pain scales were not documented during the QST performance, we did not find another parameter able to correlate the QST findings with pain levels.

Overall, more questions remain to be answered. We do not know whether the protection of myelin fibers by AT2R inhibitors is evident when these inhibitors are used prophylactically, therapeutically, or both, and we need to demonstrate a clinical correlation between CIPN symptoms and QST values. Furthermore, although our study suggested that the ARB have a better neuroprotective profile than do ACEI, we do not know which particular agent and its dose, timing, and length of therapy are needed to achieve a meaningful effect. Most likely, these questions will be need to be answered in prospective studies. We are optimistic that those answers be elucidated in our prospective study currently in design phase.

Prospective studies designed to explore the abovementioned hypothesis are needed for the population with CIPN. This would be a step forward to mechanism-based treatment for patients with this specific neuropathic pain.

Conclusions

On the basis of the QST values for touch detection thresholds, cold pain, sharp detection threshold, and cool detection threshold at the fingertip and thenar aspect of the hand, angiotensin-II type 2 receptor inhibitors might offer selective protection of small myelinated fibers of the glabrous skin in cancer patients with chemotherapy-induced peripheral neuropathy.

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