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Gastric Electrical Stimulation for Abdominal Pain in Patients with Symptoms of Gastroparesis

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Abstract

Abdominal pain physiology may be better understood studying electrophysiology, histology, and symptom scores in patients with the symptoms of gastroparesis (Gp) treated with gastric electrical stimulation (GES). Ninety-five Gp patients' symptoms were recorded at baseline and during temporary and permanent GES. Gastric-emptying times and cutaneous, mucosal, and serosal electrogastrograms were obtained. S100-stained, full-thickness gastric biopsies were compared with autopsy controls. Sixty-eight patients reported severe pain at baseline. Severe pain patients' mean pain scores decreased with temporary GES from 3.62 to 1.29 ($P < 0.001$) and nonsevere pain from 1.26 to 0.67 ($P = 0.01$). With permanent GES, severe mean pain scores fell to 2.30 ($P < 0.001$); nonsevere pain changed to 1.60 ($P = 0.221$). Mean follow-up was 275 days. Mean cutaneous, mucosal, and serosal frequencies and frequency-to-amplitude ratios were markedly higher than literature controls. For patients with Gp overall and subdivided by etiology and severity of pain, S-100 neuronal fibers were significantly reduced in both muscularis propria

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The University of Mississippi has filed an intellectual property claim regarding aspects of the technology used in this study.

layers. GES improved severe pain associated with symptoms of Gp. This severe pain is associated with abnormal electrogastrographic activity and loss of S100 neuronal fibers in the stomach's inner and outer muscularis propria and, therefore, could be the result of gastric neuropathy.

Chronic, severe abdominal pain in patients with the symptoms of gastroparesis (Gp) is a common medical reason for frequent physician and emergency department visits. Despite a complete evaluation, including upper and lower endoscopy, contrast computerized tomography, abdominal and pelvic ultrasound, and blood work, a definitive cause for this pain often is not identified. Patients with Gp symptoms who have a history of abdominal surgery may be told that their pain is the result of adhesions. Unfortunately, the use of diagnostic laparoscopy with therapeutic lysis of adhesions as a potential diagnostic and therapeutic option has not led overwhelmingly to successful symptom relief. With neither identified cause nor a reliable treatment option for chronic abdominal pain, physicians often face the dilemma of treating innumerable symptomatic, complaining patients without relying on chronic narcotic use.

Efforts to resolve many types of pain have included recourse to electrical stimulation. Such use for chronic, severe abdominal pain associated not with the symptoms of gastroparesis, however, has largely been confined to spinal stimulation. In recent years, direct electrical stimulation of the stomach, or gastric electrical stimulation (GES), has been used as an effective treatment for reducing Gp symptoms including chronic abdominal pain in patients with drug-refractory Gp, including those who on a modified Likert scale report their chronic abdominal pain as either a 3 or 4 out of 4, severe or extremely severe.[1]

Gastroparesis is a motility or physiologic failure of the stomach to fill and empty properly. This disorder results in symptoms of nausea, vomiting, early satiety and bloating, and pain may often be a symptom as well.[2] However, relatively little has been done to study the effects of GES on the subgroup of patients with Gp symptoms who experience severe, chronic abdominal pain. Our study was undertaken in an effort to correlate pain with physiologic and histologic parameters in patients with Gp symptoms as well as to contribute to a better understanding of other instances of chronic abdominal pain such as that associated with hollow viscous pain in the absence of malignancy, infection, inflammation, and distension or obstruction.

Patients and Methods

The Institutional Review Board at the University of Mississippi Medical Center approved this study. Patient consent was obtained before enrollment.

Patients

Ninety-five consecutive drug-refractory patients with the symptoms of Gp at baseline were evaluated and consented to a series of investigational and humanitarian use protocols for GES treatment. Most patients also had to demonstrate drug refractoriness and stomach mobility dysfunction through a solid-phase gastricemptying study through standardized scintigraphy and a low-fat test meal, as previously reported.[3, 4]

For the purpose of this analysis, patients, who subjectively stated their baseline abdominal pain as 0 to 2 out of 4 (no pain or mild to moderate pain), were considered the nonsevere pain group; those with scores of 3 or 4, severe or extremely severe, were considered the severe pain group.

Of the 95 patients with Gp who elected to under permanent gastric stimulator implantation (pGES), 27 (six male, 21 female; age range, 11 to 71 years; mean age, 43.9 years; 11 diabetic, 16 idiopathic) had nonsevere pain before treatment. Another 68 (nine male, 59 female; age range, 19 to 69 years; average age, 44.6 years; 22 diabetic, 46 idiopathic) had severe pain. Of the original 95 patients, 82 patients (58 with severe pain and 24 with nonsevere pain) were available for follow-up at least one month after pGES with a mean latest follow-up at 275 days after pGES implantation.

Intervention

Patients underwent at least a four-day trial of temporary gastric stimulation (Enterra, trademark of Medtronic) through an endoscopically placed gastric mucosal lead.[5] Patients who had lead dislodgment as a result of emesis or could not complete the temporary trial were excluded. Patients with a successful trial proceeded with placement of a permanent gastric electrical stimulator (Enterra) through laparotomy.[6]

At the time of pGES placement, a full-thickness gastric biopsy was also obtained from 93 patients; biopsy was contraindicated for two participants as a result of prior gastric resection or scarring. The biopsy specimen was obtained by using an end-to-end anastomosis circular stapler placed tangentially at approximately 5 cm proximal to the pylorus along the midline of the anterior surface of the stomach. A dimesized, full-thickness biopsy was removed, leaving the staple line on the serosal surface without entering the lumen. This line was imbricated with monofilament, absorbable suture to reduce adhesions.

Symptoms

Patient-reported measures of Gp symptoms describing the frequency and severity of nausea, vomiting, bloating, early satiety, and epigastric pain were quantified (0 to 4) with a modified Likert scale tool.[7] These symptom reports were collected at baseline (before electrical stimulation), at least four days after activation of temporary GES, and during the three-month and one-year follow-up visits after implantation of a pGES. Patients with suboptimal symptom response to stimulation had their devices adjusted by a previously published energy algorithm during these visits.[8]

Physiology

Gastric-emptying time (GET) and electrogastrogram (EGG) were also performed and recorded.[3] Gastric retention was documented at one-, two-, and four-hour increments by nuclear scintigraphy with delayed GET defined as a greater than 10 per cent retention (95th percentile) of a Tc 99^{m} radionuclide-labeled meal four hours after ingestion.[2] EGG measures of amplitude and frequency were assessed by using cutaneous leads at baseline, mucosal leads at temporary stimulation, and seromuscular leads during implantation of the

permanent gastric stimulator. Baseline mucosal and seromuscular EGG values were collected before the temporary or permanent GES was activated, respectively.

Histopathology

The study pathologist examined each full-thickness gastric biopsy after the sample had been immunohistologically stained with S-100 to permit identification of nerve fibers. These fibers were counted in the inner and outer muscle layers of the muscularis propria across 10 high-power fields (hpf). The counts for all 10 hpf were averaged to obtain a mean. All histologic findings were compared with findings from 17 autopsy controls.

Evaluation of gastric neuronal histology as well as of electrophysiology, gastric emptying time, and symptom scores allowed us to analyze and compare findings between patients experiencing severe pain and those with mild to moderate pain. Each group was compared with control subjects by using two-tailed, unpaired *t* tests. Results were reported in Tables 1 through 4 as mean ± standard deviation.

Results

Symptoms Table 1 shows our findings with temporary GES for all patients and subdivided into nonsevere pain and severe pain. Improvement was dramatic during temporary GES. For patients with severe pain, pain scores fell from a mean of 3.62 (0.45) to 1.29 (1.37) ($P < 0.001$). Other symptoms were also significantly reduced in all patients (see Table 1).

Table 2 also shows our findings with pGES. With pGES, pain score decreases were again noteworthy with mean pain scores for patients with severe pain reduced from a mean of 3.62 (0.45) to 2.30 (1.57) ($P < 0.001$) at a mean follow-up of 275 days. Pain symptoms in the nonsevere group increased from baseline, but these changes were not statistically significant. For all patients, other symptoms were reduced as well (see Tables 2).

Physiology

Tables 3 and 4 compare baseline gastric-emptying retention at one, two, and four hours during temporary stimulation and with permanent stimulation in all patients and in both pain subgroups. A total of 50 of our patients who received a pGES had baseline delayed gastric emptying, whereas 30 had no delay. The remaining 15 were unable to tolerate or undergo gastricemptying scintigraphy. Of those with severe pain, 36 patients had delayed gastric emptying, and 21 had nondelayed gastric emptying.

Neither temporary nor permanent GES was associated with any significant differences in gastric-emptying times for patients with severe *versus* nonsevere pain nor for patients who had a baseline delay in GET *versus* those who had not. After the implantation of pGES, modest reductions in retention were seen; however, statistically significant reductions in gastric retention were observed at the one- and two-hour measures.

Measurements of cutaneous, mucosal, and seromuscular EGG showed no statistical difference in frequency, amplitude, or frequency/amplitude ratio for patients with severe pain as compared with those with nonsevere pain (Table 5). Serosal, mucosal, and cutaneous

EGG frequencies were elevated, and frequency-to-amplitude ratio decreased when compared with literature controls.[9]

Histopathology

Table 6 shows S100 (nerve) fiber counts in the inner and outer muscle layers of patients as compared with control subjects. In all patients, inner and outer muscle layer S100 fiber counts (neuron fibers) were significantly reduced as compared with those of control subjects. This reduction was consistent in patients stratified by Gp etiology (diabetic, idiopathic) as well as by each pain subgroup.

Discussion

Electrical Stimulation and Pain Relief

Electrical stimulation can cause abdominal pain[10]; however, since 15 A.D., it has also been reported as a method for relieving it.[11] Spinal cord stimulation has been shown to provide symptom relief for a wide spectrum of pain disorders,[12] including visceral pain resulting from chronic nonalcoholic pancreatitis,[13] chronic mesenteric ischemia,[12] and intractable cancer pain.[14]

Despite these spinal cord and transcutaneous achievements in controlling visceral pain, reports on the effects of direct, visceral, end-organ stimulation for visceral pain have been rare in the spinal cord and transcutaneous electric nerve stimulation literature. By contrast, GES has been extensively examined as a therapy for gastric dysmotility and for its capacity to reduce the symptoms of gastroparesis, including pain.[1, 5, 6]

In this study, we measured both gastric-emptying time and electrogastrography for any information that these measures might provide on how GES may reduce symptoms and particularly pain.

Physiology and Pain Relief in the Context of Patients with Symptoms of Gastroparesis

Our study documented significant abdominal pain relief in patients with Gp with severe pain after temporary stimulation and permanent stimulation. Of interest, patients with nonsevere pain had a nonstatistically significant increase in abdominal pain after permanent stimulation. The other four Gp symptoms were also significantly reduced with both temporary and permanent stimulation. For patients with severe pain, improved symptom reports with GES were associated with mild improvements in gastric emptying at the one-hour and two-hour measures with permanent stimulation and at the one-hour measure during temporary stimulation. Greater GET improvements were seen with permanent stimulation in the nonsevere group. Analyzed as one cohort, our findings agree with those of O'Grady et al., who investigated the effects of GES on total symptom score, vomiting, and nausea in Gp.[1] However, our results indicate improvements for patients with Gp in both the nonsevere and severe pain groups at the one- and two-hour gastric-emptying time points, whereas the O'Grady meta-analysis of high-frequency GES for Gp only revealed a significant improvement at the four-hour interval. Additionally, these researchers observed benefits in follow-up visits after pGES implantation that included an improved sense of physical and

psychological well-being and a dramatic reduction in the need for parenteral and nonoral enteral nutrition.[1]

We also noted that the temporary GES appeared to provide numerically greater symptoms relief than permanent devices. This could be the result of a number of factors, including the location of the temporary device, which is near the submucosal plexus, compared with the permanent device, which is near the myenteric plexus. However, previous work with temporary stimulation has shown a good long-term correlation with permanent stimulation.[15]

Multiple independent centers have reported similar, successful results in patients, both adults and children, for whom medical management has failed to improve symptoms.[1, 16] In one report, stimulation was observed to be more effective than medical therapy for treating patients with the symptoms of gastroparesis.[17] In another, the survival of patients with diabetes with Gp was significantly improved by gastric stimulation.[6]

How GES reduces symptoms is not well understood. Human studies before and during gastric stimulation have shown increases in EGG amplitude, vagal activity, and positron emission tomography-imaged activity in the thalamic and caudate nuclei of the brain during chronic GES,[18] yet the demonstration of effect centrally does not imply causation, because the alterations in propagation velocity with GES may reflect enteric and/or autonomic changes induced by electrical stimulation. Recent published findings of normalization of EGG after GES treatment suggest gastric remodeling may occur with GES treatment.[19] However, this mechanism does not explain how GES seems to immediately impact symptoms within days of initiating stimulation. Clinicians also note that sometimes patients, who have responded poorly to lower GES stimulator settings, show an immediate symptom improvement when these settings are increased. Thus, stimulation may induce neuromodulation in both local end organs and in the central nervous system and thereby may play a part in the relief symptoms.

The evaluation of gastric slow wave velocity through serosal electrodes suggests that propagation velocity in patients with Gp is reduced as compared with normal literature controls.[20] The importance of gastric dysrhythmias in Gp, however, established decades ago,[21, 22] is debated. Some feel these arrhythmias are the most important factor in the onset of Gp.[23] Others authors argue that gastric electrical amplitude is also important[24] and note that GES has been shown to alter gastric electrical activity.[18] Recent studies have shown that conduction blocks in the gastroparetic stomach can be localized to specific regions[25]; however, the source of these blocks has not yet been determined.

Similarly, the role of slow wave frequency in Gp, particularly as compared with the importance of the amplitude of gastric electrical activity, is under investigation. Examinations of cutaneous, mucosal, and seromuscular EGGs in our series of patients revealed a mean frequency that was markedly higher, at greater than 5.2, than the normal frequency range of 2.7 to 3.3.[25] Frequency-to-amplitude ratio in our patient group was also markedly elevated, at greater than 26, compared with the normal range of less than 10.[25] It is likely that each of these features plays a role in gastric slow waves and that for some

patients, it is arrhythmia or abnormal frequency that serves as the primary contributor to physiologic abnormality, whereas for others, patients' low amplitude serves that role.

In our series of patients, S100 neuronal fibers were dramatically reduced as compared with controls in all patients, whether diabetic, idiopathic, or patients with nonsevere or severe pain. We observed no differences between patients with nonsevere and patients with severe pain. The relationship between patient reports of pain improvement (mean) and low neuron fibers (S100) supports the possibility that neuronal damage (neuropathy) may be the cause of gastroparetic abdominal pain, decreased slow wave amplitude, and elevated frequency-to-amplitude ratio. If this is the case, innermuscular ICC (CD117) cells, which play a vital role in excitatory and inhibitory transmission from enteric motor neurons, may increase in number as a reactive response to compensate for neuron fiber loss.[26, 27] Because ICC were not quantified in this study, further commentary on this matter will require additional investigation.

In summary, in this therapy study of patients with the symptoms of Gp, abdominal pain is associated with the loss of normal gastric motor function, abnormal electrical physiology, histologic abnormalities of neurons, and symptom relief with treatment by direct organ electrical stimulation. This may indicate that, in some instances, abdominal pain is the result of an enteric neuropathy. Because our analysis did not quantify Cajal cells, our understanding of their role in gastric motility currently remains limited.

Conclusion

Gastroparesis is a disease involving the stomach in which altered histology and physiology of the gastric neuromuscular system produces impaired motility function and debilitating symptoms, including pain, irrespective of baseline gastric-emptying values. In our study, severe abdominal pain does not seem to be a contraindication to GES found in those with severe pain who have a moderate but statistically significant reduction in pain stimuli after GES therapy as well as other Gp symptom relief. The patients with nonsevere pain appear to have a small but not statistically significant increase in abdominal pain with stimulation for reasons that are unclear.

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Table 1

Baseline and Temporary GES's Gastroparesis Scores in all Patients and those with Severe and Non-severe Pain

	All Patients			Severe Pain			Nonsevere Pain		
Symptoms	**Baseline (n = 95)**	**During Temporary GES (n = 83)**	***P* Value of Difference**	**Baseline (n = 68)**	**During Temporary GES (n = 60)**	***P* Value of Difference**	**Baseline (n = 27)**	**During Temporary GES (n = 23)**	***P* Value of Difference**
Abdominal pain score (SD)	2.95 (1.24)	1.12 (1.31)	< 0.001	3.62 (0.45)	1.29 (1.37)	< 0.001	1.26 (0.94)	0.67 (1.06)	0.01
Early satiety score (SD)	2.99 (1.21)	1.34 (1.33)	< 0.001	3.10 (1.1)	1.38 (1.32)	< 0.001	2.72 (1.45)	1.26 (1.36)	< 0.001
Distension score (SD)	2.85 (1.33)	1.07 (1.28)	< 0.001	3.15 (1.11)	1.11 (1.26)	< 0.001	2.11 (1.56)	0.98 (1.35)	0.001
Nausea (SD)	3.42 (0.86)	1.16 (1.26)	< 0.001	3.44 (0.87)	1.11 (1.27)	< 0.001	3.35 (0.83)	1.28 (1.25)	< 0.001
Vomiting (SD)	2.43 (1.38)	0.46 (1.01)	< 0.001	2.54 (1.33)	0.43 (0.91)	< 0.001	2.13 (1.48)	0.54 (1.27)	< 0.001
Total symptom score (SD)	14.63 (3.46)	5.15 (4.67)	< 0.001	16.04 (2.75)	5.13 (4.5)	< 0.001	11.63 (3.28)	4.59 (4.58)	< 0.001

GES, gastric electrical stimulation; SD, standard deviation.

Table 2

Baseline and Permanent GES's Gastroparesis Symptom Scores in all Patients and those with Severe and Non-severe Pain

	All Patients			Severe Pain			Nonsevere Pain		
Symptoms	**Baseline (n = 95)**	**During Permanent GES (n = 82)**	***P* Value of Difference**	**Baseline (n = 68)**	**During Permanent GES (n = 58)**	***P* Value of Difference**	**Baseline (n = 27)**	**During Permanent GES (n = 24)**	***P* Value of Difference**
Abdominal pain score (SD)	2.95 (1.24)	2.10 (1.58)	< 0.001	3.62 (0.45)	2.30 (1.57)	< 0.001	1.26 (0.94)	1.60 (1.51)	0.221
Early satiety score (SD)	2.99 (1.21)	1.94 (1.31)	< 0.001	3.10 (1.1)	2.02 (1.28)	< 0.001	2.72 (1.45)	1.74 (1.39)	0.005
Distension score (SD)	2.85 (1.33)	2.25 (1.66)	< 0.001	3.15 (1.11)	2.43 (1.69)	0.005	2.11 (1.56)	1.81 (1.52)	0.197
Nausea (SD)	3.42 (0.86)	2.42 (1.63)	< 0.001	3.44 (0.87)	2.64 (1.69)	< 0.001	3.35 (0.83)	1.88 (1.32)	< 0.001
Vomiting (SD)	2.43 (1.38)	1.60 (1.63)	< 0.001	2.54 (1.33)	1.84 (1.69)	0.001	2.13 (1.48)	0.98 (1.29)	0.001
Total symptom score	14.63 (3.46)	10.13 (6.02)	< 0.001	16.04 (2.75)	11.1 (6.03)	< 0.001	11.63 (3.28)	7.80 (5.27)	0.003

GES, gastric electrical stimulation; SD, standard deviation.

Table 3

Severe and Non-severe Pain Groups' Gastric Emptying Percentage at 1, 2, and 4 hour Intervals with No, Temporary, and Permanent GES

	Patients with Severe Pain			Patients with Nonsevere Pain		
GET	**Baseline (n = 57)**	**During Temporary GES (n = 41)**	**During Perm GES (n = 18)**	**Baseline (n = 23)**	**During Temporary GES (n = 15)**	**During Perm GES (n = 15)**
1 hour (SD)	70% (20)	64% (21)	62% (22)	64% (22)	62% (22)	57% (14)
2 hours (SD)	48% (23)	43% (26)	42% (23)	40% (20)	38% (19)	29% (16)
4 hours (SD)	24% (24)	23% (25)	23% (24)	15% (11)	18% (15)	10% (14)

GET, gastric-emptying time; GES, gastric electrical stimulation; SD, standard deviation.

Table 4

All Patients' Gastric Emptying Percentage with No, Temporary, and Permanent GES

	GET: All Patients				
GET	**Baseline (n = 80)**	**During Temporary GES (n = 56)**	***P* Value**	**During Permanent GES (n = 33)**	***P* Value**
1 hour (SD)	68% (21)	64% (21)	0.14	60% (19)	0.001
2 hours (SD)	46% (23)	41% (24)	0.24	37% (21)	0.002
4 hours (SD)	21% (21)	21% (22)	0.68	17% (21)	0.31

GET, gastric-emptying time; GES, gastric electrical stimulation; SD, standard deviation.

Table 5

Cutaneous, Mucosal, and Serosal Electrogastrogram Readings in all Patients and the Subgroups of Severe and Non-severe Pain

	EGG Frequency			EGG Amplitude			EGG Frequency-to-Amplitude Ratio		
EGG	**All Patients**	**Patients with Nonsevere Pain**	**Patients with Severe Pain**	**All Patients**	**Patients with Nonsevere Pain**	**Patients with Severe Pain**	**All Patients**	**Patients with Nonsevere Pain**	**Patients with Severe Pain**
Cutaneous mean (SD); no.	5.26 (1.77); 81	5.11 (1.63); 21	5.31 (1.83); 60	0.14 (0.15); 81	0.15 (0.20); 21	0.13 (0.13); 60	74.56 (70.96); 81	72.84 (65.71); 21	75.2 (73.3)
Median (range)	4.8 (2.8–10.5)	4.63 (3.13–8.3)	4.85 (2.8–10.5)	0.1 (0.02–0.9)	0.13 (0.02–0.9)	0.1 (0.02–0.68)	48.78 (4.33–4.35)	52.2 (4.33–29)	47.8 (7.7–43.5)
P value (non-/severe pain)			0.646			0.674			0.894
Mucosal mean (SD); no.	5.14 (2.07); 40	4.54 (1.77); 12	5.40 (2.17); 28	0.81 (0.97); 40	1.07 (1.30); 12	0.70 (0.79); 28	26.37 (34.71); 40	20.76 (27.98); 12	26.5 (43.0)
Median (range)	4.45 (2.17–11.67)	4.28 (3–9.25)	5.1 (2.17–11.67)	0.37 (0.06–4.6)	0.62 (0.1–4.6)	0.36 (0.06–3.1)	13.16 (0.76–122)	6.23 (0.76–92.5)	7.0 (1.7–215)
P value (non-/severe pain)			0.199			0.375			0.375
Serosal mean (SD); no.	5.60 (1.8); 82	5.48 (1.69); 22	5.64 (1.8); 60	0.47 (0.52); 82	0.47 (0.48); 22	0.47 (0.53)	32.35 (44.13); 82	32.28 (59.43); 22	32.4 (37.6)
Median (range)	5.5 (2.93–14.7)	5 (3.25–9.67)	5.55 (2.93–14.7)	0.31 (0.02–2.33)	0.32 (0.02–1.92)	0.28 (0.05–2.33)	16.77 (2.0–280)	13.62 (3.56–280)	19.2 (2.0–160)
P value (non-/severe pain			0.714			0.998			0.994

EGG, electrogastrogram; SD, standard deviation.

Table 6

Histologic S100 (Nerve) Fiber Counts in the Inner and Outer Gastric Muscle Layers by Gastroparesis Etiology and Pain Severity

	S100					
S100	**Controls (n 4 17)**	**All (n 4 93)**	**Diabetes Mellitus (n 4 33)**	**Idiopathic (n 4 60)**	**Nonsevere Pain (n 4 26)**	**Severe Pain (n 4 67)**
Outer						
Mean (SD)	19.2 (11.9)	7.4 (5.9)	6.6 (4.4)	7.8 (6.6)	7.8 (5.8)	7.2 (6.0)
Median (range)	14.8 (5.9–46.8)	6 (1–40)	6.0 (1–19)	5.8 (1–40)	5.5 (0.9–23.6)	6.0 (1–40)
P value		0.0009	0.0005	0.0013	0.0014	0.0008
Inner						
Mean (SD)	26.8 (19.5)	13.3 (9.7)	14.5 (9.6)	12.6 (9.7)	15.5 (9.3)	12.5 (9.8)
Median (range)	24.5 (8.8–88.3)	10 (2–46)	12.3 (3–42)	9.4 (2–46)	12.2 (5.5–37)	9.3 (2–46)
P value		0.0155	0.0288	0.012	0.0426	0.0112

SD, standard deviation.