# Topical application of Gel saturated with Nanobubbles of $O_2$ and $CO_2$ for the treatment of Diabetic Peripheral Neuropathy.

[1]Douglas J. Grimm, DPM; [2]Jeffery W. LaMour, DPM; [3]Scott T. Pattison, DPM; [4]Keith C. McSpadden, DPM; Jean A. Woloszko[5] MD PhD

1: Foot Associates Central Texas, Round Rock, TX. 2: Family Foot Care, Austin, TX. 3: Foot Associates Central Texas, Georgetown, TX. 4: North Austin Foot & Ankle Institute, Cedar Park, TX 5: PeriphEX Corp., Austin TX

## Abstract

Diabetic Peripheral Neuropathy (DPN) is frequently associated with hypoxia and inflammation of peripheral nerve structures. Nanobubbles of Oxygen can diffuse deeply through tissues and reduce cell hypoxia and inflammation. The interim results of this multicenter prospective cohort observational study for patients suffering from diabetic peripheral neuropathy (DPN) demonstrates that repeated topical applications of a gel loaded with nanobubbles of $O_2$ and $CO_2$ are effective at providing a relief of the symptoms and improving quality of life.

## Literature Review

In the United States, 70-80% of 20 million people with diabetes suffer from peripheral neuropathy. Another 25% of the 80 million people with prediabetes also suffer from peripheral neuropathy (1). Therefore, over thirty million neuropathic people, have diabetes or pre-diabetes.

Selecting a treatment option that is both effective and well tolerated can be challenging. Overall, many patients are dissatisfied with their current treatment and are actively looking for better solutions.

Peripheral nerve hypoxia resulting from both the diabetic vasculopathy and hyperglycemia has been associated with DPN (2). Nanobubbles of gas are bubbles 50 to 200 nm in size that are very stable, can be in solution in high concentration, and can easily diffuse into soft tissues. Nanobubbles of oxygen can reduce cellular hypoxia (3) and possess anti-inflammatory and neuroprotective properties (4). Owen at al. (5) have also shown that systemic $O_2$ nanobubbles can reduce cellular hypoxia and their expression of hypoxia-inducible-factor-1α (HIF1α) protein. LaMour (5) demonstrated that topical applications of $O_2$ and $CO_2$ nanobubbles solution can effectively reduce pain in peripheral neuropathy of various etiologies.

## Statement of Purpose:

The multicenter prospective IRB-approved observational study's primary aim is to evaluate the safety and efficacy of repeated topical applications of hydrogel saturated with $O_2$ and $CO_2$ nanobubbles (NoxyPure, PeriphEX Corp.) for the treatment of DPN.

## Methodology and Procedure

Patients with diabetes with painful DPN with at least some hypoesthesia and no interfering pathologies are treated in the office with ten consecutive 20-minute treatments. Patients are evaluated at baseline, before each treatment, and less than1 week, and 1 month after the 10th treatment.

Evaluations include validated pain questionnaires (usual and peak pain over a 24h period), the Semmes-Weinstein 5.07 (10 g) Monofilament Examination, the modified Toronto Neuropathy Score, and a Quality of Life questionnaire.

**Photo 1: nanobubbles saturated gel treatment delivery setup**

## Level of Evidence

Level IV. Therapeutic

## Results and Discussion

All 22 patients enrolled by 4 sites in the study as of October 31, 2019 were included in the safety analysis. Only 14 patients are included in the efficacy analysis; we did not include 3 patients lost to follow-up before completing the 10 treatments and 5 patients who have not yet completed the 10 treatments.

One adverse event was reported: a patient reported improved symptoms in his feet but felt increased pain in his calves above the treated area and decided to voluntarily withdraw from the study after 4 treatments. His pain resolved a few days later.

| N=14 | Mean ± standard deviation |
|---|---|
| Age | Mean: 71.8 ±5.34 (63 – 82) |
| Gender | Females: 6 (42.9%)<br>Males: 8 (57.1%) |
| Total Treatment Duration | Mean: 29.3 ±6.29 (20.5 – 41.6) days |
| Time between treatments | Mean: 3.3±2.64 (0.4-20.4) Days<br>Mode: 2 Days |
| Interval last treatment to 1 week follow-up | Mean: 5.2 ±2.54 (.4 –7.4) |
| Interval last treatment to 1 month follow-up | Mean: 32.1 ±5.81 (27.4-43.5) Days |

**Table 1: Demographics**

| | Baseline | After 6 treatments | After 10 treatments | 1 Month Follow-up |
|---|---|---|---|---|
| Pain During Day | 12 (86%) | 11 (79%) | 8 (57%) | 10 (71%) |
| Pain during Night | 11 (79%) | 10 (71%) | 9 (64%) | 10 (71%) |
| Shooting Pain | 5 (36%) | 2 (14%) | 1 (7%) | 4 (29%) |
| Electric Shock | 14 (100%) | 10 (71%) | 7 (50%) | 9 (64%) |
| Burning | 5 (36%) | 2 (14%) | 0 (0%) | 1 (7%) |

**Table 2: Presence of Pain**

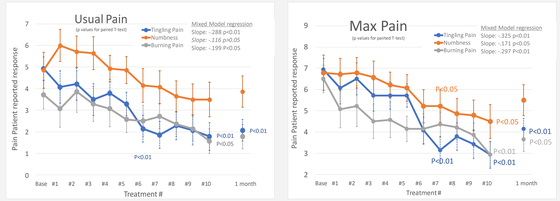


**Figure 1: Patients Reported Maximum and Usual Pain levels with treatments.**

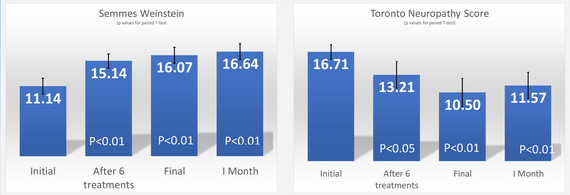


**Figure2: Semmes-Weinstein Test results**




**Figure3: Toronto Neuropathy Scores**


**Figure 4: Quality of Life questionnaire**

**Pain:** The mean improvement of tingling pain was 58% for max and usual pain (paired T-test, P<0.001). Improvement was reported at 58% (P<0.05) and 55% (P<0.01) for usual and max burning pain. While 35% of the patients complained of burning at baseline, none of them complained of burning pain after the 10th treatment. With 71% and 50% of the patients respectively, reporting at least 50% reduction in the usual tingling and burning pain respectively, the effectiveness of the Nanobubbles compare favorably to some results reported with Gabapentin (7) or Pregabalin (8) with 50% or more pain reduction in 40% and 27% of the patients, respectively.

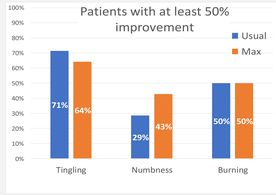


**Figure 5: Patients with at least 50% improvement**

**Sensitivity:** There seems to be relatively poor correlation between the Semmes-Weinstein (SW) and patient reported Numbness Score; 85% and 93% of the patients had an improved SW score after 6 and 10 treatment respectively, but only 50% and 57% of the patients reported an improved reported subjective Usual Numbness score after 6 and 10 treatments. 35% of the patients reported more "Numbness Pain" after the first treatment. After 10 treatments, the overall improvements were 28% and 34% for usual and max numbness pain, and 44% for the more objective S-W test.

Overall, pain, sensitivity, quality of life and Toronto Neuropathy score all improved after 6 and 10 treatments of topical applications of nanobubbles of $O_2$ and $CO_2$. While one month after the last treatment some of the effects dissipate, significant gains remain. We believe that a periodic treatment regimen would be able to maintain improvements over time. This will be evaluated at the six-month follow-up of this study. Patients will be examined after they had the opportunity to self-administer at home as many treatments as they felt necessary after their one-month follow-up.

## Conclusion:

In an interim analysis of 14 patients suffering from Diabetic Peripheral Neuropathy, we show that 10 successive topical applications of nanobubbles loaded hydrogel provide significant improvement of pain, sensitivity, neuropathy score, and quality of life. These improvements last several weeks after the end of the last treatment. Results should be confirmed by the analysis of a larger sample size and over an extended trial time. Evidence suggests that topical application of NoxyPure (PeriphEX Corp., Austin, TX), a hydrogel saturated with nanobubbles of $O_2$ and $CO_2$ should be considered as a safe and effective alternative treatment for Diabetic Peripheral Neuropathy.

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## Financial disclosure

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