2015

Decreased Pain Severity and Differential Gene Expression Following Calmare Therapy

Jeffrey Petraco
Virginia Commonwealth University, petracojb@vcu.edu

Angela R. Starkweather
Virginia Commonwealth University

Amy Heineman
Virginia Commonwealth University, s2aheine@vcu.edu

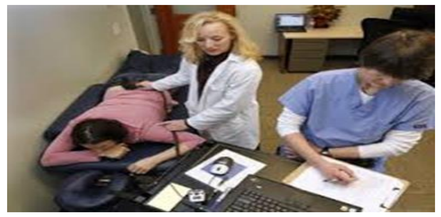
VIRGINIA COMMONWEALTH UNIVERSITY

Decreased Pain Severity and Differential Gene Expression Following Calmare Therapy

Amy Heineman, BSN, RN, STAR Project Director, Jeffrey B. Petraco, MBA, RN and Angela Starkweather, Ph.D., ACNP-BC, CNRN, Associate Professor and Chair, Adult Health and Nursing Systems Department

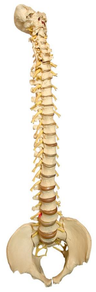
Abstract

We present the results of a double-blinded randomized sham-controlled research study of a non-pharmacologic low back pain intervention. Calmare therapy is an neurocutanous electrical stimulation approach for pain management. The intervention group received Calmare therapy and the other received sham. Differences in pain severity and interference scores, pain sensitivity measures and gene expression profiles are reported. Patterns of downregulated gene expression suggest that Calmare may alter proteins involved in pain transduction may have implications for the treatment of other chronic pain conditions.



Introduction

- Persistent low back pain (LBP) is one of the nation's most expensive medical conditions and a leading cause of disability.
- Several lines of evidence support the premise that LBP develops as a consequence of sensitization of nociceptors and neuronal circuits with modifications in the expression of genes that encode pain signaling molecules and their receptors.
- Gene associated with neurotropins, inflammatory mediators and catecholamines are most often modified.
- Calmare, a non-invasive bioengineering-based method of pain treatment, was designed to interrupt the mechanisms of persistent pain by scrambling the pain signaling using electrical waveforms that mimic endogenous action potentials.
- A double–blinded randomized sham controlled pilot study was conducted at VCU School of Nursing. Persistent LBP was defined as pain without a specific cause or need for surgical intervention in the region of the low back below T2 and above the buttock crease, persistent for at least or more than 3 months for more than or equal to 4 days a week at a level of 4 or greater. Participants received a standard protocol of Calmare or sham using the Calmare device to deliver a non-therapeutic threshold. Data collected included study questionnaires, quantitative sensory testing (QST), and blood samples.



Results/Discussion

There was a statistically significant difference in the "worst" pain score between the Calmare and sham groups at the 1 and 3 week follow-up visits. Pain interference was significantly different between groups at the 3 week follow-up visit, with significantly lower pain interference in the Calmare group. The "worst" pain and interference scores of the BPI showed a significant decrease in the Calmare group from baseline to the 3 week follow-up visit whereas the sham treatment group did not change over time. In the Calmare group, 7 (47%) participants had a ≥50% reduction in the "worst" pain score from baseline to the 3-week follow-up visit, 5 (33%) participants had a 30-49% reduction, and 3 (20%) had a 20-29% reduction.

Measures of pain sensitivity (heat pain threshold, single stimulus rating, and pressure pain threshold) were significantly different between groups at the 3 week follow-up visit. The higher level thresholds to heat pain and pressure pain in the Calmare group at 3 weeks follow-up reflect that a higher stimulus intensity is required to cause a perception of pain. Consistent with these findings, they also rated their perception of pain lower to the single heat stimulus. These findings demonstrate less pain sensitivity in the Calmare group compared to the sham group at the 3 week follow-up visit. However, the within group changes in pain sensitivity measures from baseline to 3 weeks did not reach a level of statistical significance.

There were no significant differences in the baseline mRNA levels of the 84 candidate genes between the Calmare and sham groups. However, differential expression of 17 candidate genes was observed between baseline and 3 weeks post-intervention. Using a p-value threshold of <0.01, the fold regulation of these genes were significantly different between the Calmare and sham group: *BDKRB1, CACNA1B, CCKBR, CHRNA4, GDNF, GRM1, HTR2A, KCNIP3, KCNQ2, NGF, NTRK1, OPRD1, OPRK1, OPRM1, PENK, PLA2G1B,* and *TAC1*. The table below shows the differential fold regulation in the Calmare group at 3 weeks post-intervention accompanied by the associated p-value.

Differential Gene Expression in the Calmare Group at 3 Weeks Post-Treatment

Gene	Fold Regulation	p-value
BDKRB1	-2.468	0.0069
CACNA1B	-1.518	0.0091
CCKBR	-1.804	0.0150
CHRNA4	-1.924	0.0053
GDNF	-2.141	0.0036
GRM1	-1.715	0.0033
HTR2A	-2.630	0.0100
KCNIP3	-2.587	0.0100
KCNQ2	-1.550	0.0172
NGF	-2.599	0.0040
NTRK1	-1.980	0.0035
OPRD1	-1.812	0.0049
OPRK1	-2.083	0.0110
OPRM1	-1.699	0.0100
PENK	-1.850	0.0042
PLA2G1B	-1.816	0.0020
TAC1	-1.852	0.0150

Conclusion

The results of this study suggest that Calmare provides significantly more pain relief than sham at 3 weeks post-intervention and can reduce pain intensity, interference and pain sensitivity in individuals with persistent low back pain. The differential expression of pain genes between the intervention and sham group suggests that it may exert an effect by downregulating pain receptors and proteins involved in maintaining persistent pain. Evaluation of long-term outcomes after Calmare, particularly functional status, analgesic use and health care utilization, is warranted in future studies.

Works Cited

Coyne, P. J., Wan, W., Dodson, P., Swainey, C., & Smith, T. J. (2013). A trial of Calmare therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *Journal of Pain & Palliative Care Pharmacotherapy, 27*(4), 359-364.

Emery, E. C., Young, G. T., Berrocoso, E. M., Chen, L., McNaughton, P. A. (2011). HCN2 ion channels play a central role in inflammatory and neuropathic pain. *Science, 333*, 1462-1466.

Fang, J. F., Liang, Y., Du, J. Y., & Fang, J. Q. (2013). Transcutaneous electrical nerve stimulation attenuates CFA-induced hyperalgesia and inhibits spinal ERK1/2-COX-2 pathway activation in rats. *BMC Complementary and Alternative Medicine, 13*, 134.

(*Selected references above; full list of references available upon request.*)

Acknowledgements

Components of this project were supported by the National Institute of Nursing Research through grant #P30 NR011403 (MJ Grap, PI). Dr. Starkweather (R01 NR013932) is currently receiving research funding from the National Institute of Nursing Research, National Institutes of Health. The content of this poster is solely the responsibility of the authors and does not represent the official views of the National Institute of Nursing Research or the National Institutes of Health. The trial was registered on clinicaltrials.gov under NCT01896687.