

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of high-voltage pulsed radiofrequency ablation versus standard-voltage pulsed radiofrequency ablation for patients with neuropathic pain: protocol for a systematic review and meta-analysis
AUTHORS	Jia, Yitong; wang, zheng; Ma, Yanhui; Wang, Tengting; Feng, Kunpeng; Feng, Guang; Wang, Tianlong

VERSION 1 – REVIEW

REVIEWER	Silva-Ortiz, Victor Hospital Zambrano Hellion, Pain Management
REVIEW RETURNED	18-Apr-2022

GENERAL COMMENTS	<p>It is a very interesting and promising topic in the treatment of neuropathic pain, however, I have some questions and some suggestions.</p> <ol style="list-style-type: none">1. Do you have a table that describes the characteristics of the papers used for a better understanding of what you are analyzing?2. On the other hand, there is more related to the topic that they are not including in this manuscript and I am concerned that this revision is not robust. <p>There is an interesting article comparing high vs. standard voltage that they are not citing in this manuscript.</p> <p>Fang L, Tao W, Jingjing L, Nan J. Comparison of High-voltage- with Standard-voltage Pulsed Radiofrequency of Gasserian Ganglion in the Treatment of Idiopathic Trigeminal Neuralgia. <i>Pain Pract.</i> 2015 Sep;15(7):595-603. doi: 10.1111/papr.12227. Epub 2014 Jun 23. PMID: 24954016.</p> <p>Zipu et al. also wrote a follow-up of 149 patients with interesting results according to the dose of PRF. After the original article, a letter to the editor is published to explain what dose of PRF was applied to patients who did not respond and a second PRF procedure was applied, finding that a higher dose was applied than the initial one with which symptoms improved.</p> <p>Zipu J, Hao R, Chunmei Z, Lan M, Ying S, Fang L. Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients. <i>Pain Physician.</i> 2021 Dec;24(8):E1263-E1271. PMID: 34793653.</p> <p>Silva V. Comments on "Long-term Follow-up of Pulsed</p>
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	<p>Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". Pain Physician. 2022 Mar;25(2):E408. PMID: 35323002.</p> <p>Fang L, Jia Z. In Response to Comments on "Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". Pain Physician. 2022 Mar;25(2):E409. PMID: 35323003.</p>
REVIEWER	Mccarthy, Robert Rush University Medical Center, Anesthesiology
REVIEW RETURNED	22-Apr-2022
GENERAL COMMENTS	<p>It is of concern to me that there will be enough RCT trials of both high-voltage as well as standard-voltage pulsed radiofrequency nerve ablation to make meaningful conclusion from the meta-analysis. I believe that the literature search represents preparatory work in order to do apply the meta-analytical techniques. Could the authors provide a list of papers that have been found to meet the criteria for the study? This number would be helpful in determining if there is enough available RCT's to perform a meaningful analysis. Second, pulsed radiofrequency is still radiofrequency nerve ablation and should be labeled as such throughout the manuscript. The differences in the mechanisms of the PRF and continuous RF are still a topic for consideration.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: It is a very interesting and promising topic in the treatment of neuropathic pain, however, I have some questions and some suggestions.

1. Do you have a table that describes the characteristics of the papers used for a better understanding of what you are analyzing?

Response: Thank you for your constructive advice. We have added table 1 which describes the characteristics of the papers in our newly submitted files.

2. On the other hand, there is more related to the topic that they are not including in this manuscript, and I am concerned that this revision is not robust.

There is an interesting article comparing high vs. standard voltage that they are not citing in this manuscript.

Fang L, Tao W, Jingjing L, Nan J. Comparison of High-voltage- with Standard-voltage Pulsed Radiofrequency of Gasserian Ganglion in the Treatment of Idiopathic Trigeminal Neuralgia. Pain Pract. 2015 Sep;15(7):595-603. doi: 10.1111/papr.12227. Epub 2014 Jun 23. PMID: 24954016.

Zipu et al. also wrote a follow-up of 149 patients with interesting results according to the dose of PRF. After the original article, a letter to the editor is published to explain what dose of PRF was applied to patients who did not respond and a second PRF procedure was applied, finding that a higher dose was applied than the initial one with which symptoms improved.

Zipu J, Hao R, Chunmei Z, Lan M, Ying S, Fang L. Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients. Pain Physician. 2021 Dec;24(8):E1263-E1271. PMID: 34793653.

Silva V. Comments on "Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". Pain Physician. 2022 Mar;25(2):E408. PMID: 35323002.

Fang L, Jia Z. In Response to Comments on "Long-term Follow-up of Pulsed Radiofrequency

Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". Pain Physician. 2022 Mar;25(2):E409. PMID: 35323003.

Response: We are very grateful for your valuable comments. The articles you shared with us are all interesting and constructive papers and we have cited these papers in our revised manuscript. The following sentences are the content we added in our revised article according to your advice.

Afterwards, Luo et al compared the efficacy of high-voltage PRF with standard-voltage PRF for idiopathic trigeminal neuralgia (TN) patients who responded poorly to oral carbamazepine or nerve blockade by steroid, and the results revealed the 1- year effective rate of high-voltage PRF (69%) was significantly higher than that in the standard-voltage PRF treatment (19%) (P = 0.000).18

Jia et al retrospectively analyzed the medical data of patients with idiopathic TN undergoing PRF. The study found that for patients who did not respond to the first PRF treatment and underwent the second PRF treatment, a higher dose of out-put voltage than the initial one could achieve improved analgesic effect.20-22

18. Radiofrequency of Gasserian Ganglion in the Treatment of Idiopathic Trigeminal Neuralgia. Pain practice : the official journal of World Institute of Pain 2015;15(7):595-603. doi: 10.1111/papr.12227 [published Online First: 2014/06/24]

20. Fang L, Jia Z. In Response to Comments on "Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". Pain physician 2022;25(2):E409. [published Online First: 2022/03/25]

21. Silva V. Comments on "Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients". Pain physician 2022;25(2):E408. [published Online First: 2022/03/25]

22. Zipu J, Hao R, Chunmei Z, et al. Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients. Pain physician 2021;24(8):E1263-e71. [published Online First: 2021/11/19]

Reviewer #2

1. It is of concern to me that there will be enough RCT trials of both high-voltage as well as standard-voltage pulsed radiofrequency nerve ablation to make meaningful conclusion from the meta-analysis. I believe that the literature search represents preparatory work in order to do apply the meta-analytical techniques. Could the authors provide a list of papers that have been found to meet the criteria for the study? This number would be helpful in determining if there is enough available RCT's to perform a meaningful analysis.

Response: Thanks for your comments. To our knowledge, there are 6 RCT trials for comparing the efficacy and safety of high-voltage pulsed radiofrequency with standard-voltage pulsed radiofrequency for patients with neuropathic pain. And the papers meeting the criteria for our study are listed below.

(1) Fang L, Tao W, Jingjing L, et al. Comparison of High-voltage- with Standard-voltage Pulsed Radiofrequency of Gasserian Ganglion in the Treatment of Idiopathic Trigeminal Neuralgia. Pain Practice : the official journal of World Institute of Pain 2015;15(7):595-603. doi: 10.1111/papr.12227 [published Online First: 2014/06/24]

(2) Luo F, Wang T, Shen Y, et al. High Voltage Pulsed Radiofrequency for the Treatment of Refractory Neuralgia of the Infraorbital Nerve: A Prospective Double-Blinded Randomized Controlled Study. Pain physician 2017;20(4):271-79. [published Online First: 2017/05/24]

(3) Han Z, Hong T, Ding Y, Wang S, Yao P. CT-Guided Pulsed Radiofrequency at Different Voltages in the Treatment of Postherpetic Neuralgia. Frontiers in neuroscience. 2020; 14:579486.

(4) Wan CF, Song T. Comparison of Two Different Pulsed Radiofrequency Modes for Prevention of Postherpetic Neuralgia in Elderly Patients with Acute/Subacute Trigeminal Herpes Zoster. Neuromodulation : journal of the International Neuromodulation Society 2021 doi: 10.1111/ner.13457 [published Online First: 2021/05/20]

(5) Li H, Ding Y, Zhu Y, Han Z, Yao P. Effective Treatment of Postherpetic Neuralgia at the First

Branch of the Trigeminal Nerve by High-Voltage Pulsed Radiofrequency. *Frontiers in neurology*. 2021;12:746035.

(6) Wang B, Du Z, Xia J, Zhang H. Efficacy of High-Voltage Pulsed Radiofrequency for the Treatment of Elderly Patients with Acute Herpes Zoster Neuralgia. *Revista da Associacao Medica Brasileira* (1992). 2021;67(4):585-589.

2. Second, pulsed radiofrequency is still radiofrequency nerve ablation and should be labeled as such throughout the manuscript. The differences in the mechanisms of the PRF and continuous RF are still a topic for consideration.

Response: Thank you for your helpful comments. We appreciate your keen observation. We feel so sorry that our previous description was not accurate, and we have changed “pulsed radiofrequency” into “pulsed radiofrequency ablation” throughout the manuscript according to your suggestion. In recent years, radiofrequency nerve ablation has applied as a novel nonpharmacological technique for the treatment of neuropathic pain. There are two types of radiofrequency nerve ablation, conventional radiofrequency ablation (CRF) and pulsed radiofrequency (PRF). CRF is a destructive treatment that generates a temperature of 60°C to 80°C and causes selective thermocoagulation of pain-carrying nerve fibers (A- δ and C fibers), thereby interrupts the transmission of pain signals¹. PRF ablation provides a continuous current action of 20 ms followed by an intermission period of 480 ms and the heat could be dissipated by thermal conductance into the surrounding area within the quiet period, and the temperature will not exceed 42°C². The mechanism of PRF treatment is via the modulation of nerve function caused by the electric field effect rather than blocking pain signal transduction⁴. Up to now, there are a few published randomized controlled trials (RCTs) comparing the efficacy of CRF versus PRF in the treatment of trigeminal neuralgia⁵, lumbar facet syndrome⁶, facet joint low back pain⁷, as well as chronic perineal pain⁸. A systematic review and meta-analysis remain to be conducted to furtherly compare the analgesic effect and safety of CRF and PRF for the treatment of chronic pain.

1. Heavner JE, Boswell MV, Racz GB. A comparison of pulsed radiofrequency and continuous radiofrequency on thermocoagulation of egg white in vitro. *Pain physician* 2006;9(2):135-7. [published Online First: 2006/05/18]

2. Vuka I, Marciuš T, Došenović S, et al. Efficacy and Safety of Pulsed Radiofrequency as a Method of Dorsal Root Ganglia Stimulation in Patients with Neuropathic Pain: A Systematic Review. *Pain medicine (Malden, Mass)* 2020;21(12):3320-43. doi: 10.1093/pm/pnaa141 [published Online First: 2020/06/04]

3. Zipu J, Hao R, Chunmei Z, et al. Long-term Follow-up of Pulsed Radiofrequency Treatment for Trigeminal Neuralgia: Kaplan-Meier Analysis in a Consecutive Series of 149 Patients. *Pain physician* 2021;24(8):E1263-e71. [published Online First: 2021/11/19]

4. Martin DC, Willis ML, Mullinax LA, et al. Pulsed radiofrequency application in the treatment of chronic pain. *Pain practice : the official journal of World Institute of Pain* 2007;7(1):31-5. doi: 10.1111/j.1533-2500.2007.00107.x [published Online First: 2007/02/20]

5. Elawamy A, Abdalla EEM, Shehata GA. Effects of Pulsed Versus Conventional Versus Combined Radiofrequency for the Treatment of Trigeminal Neuralgia: A Prospective Study. *Pain physician* 2017;20(6):E873-e81. [published Online First: 2017/09/22]

6. Kroll HR, Kim D, Danic MJ, et al. A randomized, double-blind, prospective study comparing the efficacy of continuous versus pulsed radiofrequency in the treatment of lumbar facet syndrome. *Journal of clinical anesthesia* 2008;20(7):534-7. doi: 10.1016/j.jclinane.2008.05.021 [published Online First: 2008/12/02]

7. Tekin I, Mirzai H, Ok G, et al. A comparison of conventional and pulsed radiofrequency denervation in the treatment of chronic facet joint pain. *The Clinical journal of pain* 2007;23(6):524-9. doi: 10.1097/AJP.0b013e318074c99c [published Online First: 2007/06/19]

8. Usmani H, Dureja GP, Andleeb R, et al. Conventional Radiofrequency Thermocoagulation vs Pulsed Radiofrequency Neuromodulation of Ganglion Impar in Chronic Perineal Pain of Nononcological Origin. *Pain medicine (Malden, Mass)* 2018;19(12):2348-56. doi: 10.1093/pm/pnx244 [published Online First: 2018/01/13]

VERSION 2 – REVIEW

REVIEWER	Silva-Ortiz, Victor Hospital Zambrano Hellion, Pain Management
REVIEW RETURNED	07-Jun-2022

GENERAL COMMENTS	The additional information improves the paper.
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REVIEWER	Mccarthy, Robert Rush University Medical Center, Anesthesiology
REVIEW RETURNED	01-Jun-2022

GENERAL COMMENTS	The authors have address my questions.
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