Evidence-Based Practice Group Answers to Clinical Questions

"Efficacy and/or Effectiveness of Portable Neuromodulation Stimulator (PoNS®) as Treatment for Traumatic Brain Injury (TBI)"

A Rapid Systematic Review

By

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Clinical Services – Worker and Employer Services

About this report

Efficacy and/or Effectiveness of Portable Neuromodulation Stimulator (PoNS®) as Treatment for Traumatic Brain Injury (TBI)

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Objective

To determine whether or not there is evidence to support the efficacy and/or effectiveness of the Portable Neuromodulation Stimulator (PoNS®) as treatment for patients with traumatic brain injuries, in particular, for balance and gait.

Methods

- A comprehensive systematic literature search was conducted on October 9, 2019.
- The search was done on commercial medical literature databases, including Cochrane Database of Systematic Reviews® (2005 to October 3, 2019), ACP Journal Club® (1991 to September 2019), UK York University Database of Abstracts of Reviews of Effects® (1st Quarter 2016), Cochrane Clinical Answers® (August 2019), Cochrane Central Register of Controlled Trials® (September 2019), UK NHS Health Technology Assessment® (4th Quarter 2016), UK NHS Economic Evaluation Database® (1st Quarter 2016), BIOSIS Previews® (1969 to 2008), Embase® (1974 to 2019 October 08), Medline Epub Ahead of Print®, Medline In-Process & Other Non-Indexed Citations®, Medline Daily Update® and Medline® (1946 to October 08, 2019), that are available through the Ovid® platform.
- The search was done by employing combinations of keywords. We started with very specific keyword combinations and then expanding to more general ones.
  These keywords include:
  1. (Portable **ADJ** Neuromodulation **ADJ** Stimulator) **OR** (PoNS **AND** Heuro) **OR** (PoNS **AND** (Helius **ADJ** Medical)) **AND** ((traumatic **ADJ** brain **ADJ** injury) **OR** balance **OR** gait **OR** (balance **ADJ** deficit))
  2. (Portable **ADJ** Neuromodulation **ADJ** Stimulator) **OR** (PoNS **AND** Heuro) **OR** (PoNS **AND** (Helius **ADJ** Medical))
- No limitations, such as on the language, date or type of publication, were implemented in any of these searches.
- A manual search was also conducted on the references of the articles that were retrieved in full.
- In an attempt to identify randomized/control trials conducted on the device, we also searched the websites of the US National Library of Medicine clinicaltrials.gov (https://clinicaltrials.gov/) for studies on PoNS®. The search was done by employing combinations of the keywords "Portable Neuromodulation Stimulator" within the "Other Terms" field on the search page of this website. Only registered trials with results posted on the website were retrieved for further appraisal. There were 11 clinical

trials found within this search (conducted on October 10, 2019). At the time of the search, of these 11 trials, three trials were withdrawn, five trials were still recruiting and three trials were completed, two of which posted results[13,14].

Results

- Search results:
  - Eleven[1-8,10-12] published studies were identified from search No.1, with search No.2 returning one[9] study. Hence, overall, there were 12[1-12] published studies identified through the literature searches. Upon examination of the titles and abstracts of these twelve[1-12] studies, eleven[2-12] studies were thought to be relevant and were retrieved in full for further appraisal. Of these 11[2-12] studies, only three[2,4,6] studies were published in full report format while the rest were published as abstract-only format, as part of proceedings of conferences.
  - Of these 11[2-12] studies that were retrieved in full, four[3,5,7,9] will not be discussed further since two did not provide any data[5,9] and two[3,7] were duplicate publications using the same data set.
  - Two[13,14] clinical trials, with results, were identified from the www.clinicaltrials.gov website. One of the trials was a randomized controlled trial on TBI[13] and the other one was a small case series on patients with multiple sclerosis[14].
  - As such, overall, there are nine[2,4,6,8,10,11,12,13,14] studies that are going to be appraised and summarized below.
  - No additional study was identified from the manual searches.
- In a case report (level of evidence 5. Appendix 1) Bastany et al.[2] reported the efficacy of a treatment programme using high-intensity physiotherapy and supplemented with PoNS®, in the case of a patient with cerebellar degeneration. Although Bastani et al.[2] reported that the patient improved in her gait and balance without any adverse effects, the results were measured shortly after the end of the intervention (at week 12), with no further long term results reported.
- In a small case series (n=2) (level of evidence 5. Appendix 1), Chisholm et al.[4] reported the potential application of PoNS® in balance and gait training towards improving the functional outcomes in people with incomplete spinal cord injury (C-5 and T 5-6 level of injury). At the completion of 12 weeks of balance and gait training augmented with PoNS®, the authors found improved measures for the standing balance with eyes closed, balance confidence, ground-walking speed, as well as skilled walking functions. Although the authors concluded that PoNS® combined with task-specific training was a feasible method for improving balance and gait in people with

incomplete spinal cord injury, it should be noted that these outcomes were measured at just 24 weeks post-intervention with no longer term data reported.

- A small randomized double-blinded controlled trial (total n=14) (level of evidence 1. Appendix 1) investigating the effects of non-invasive tongue stimulation using PoNS® combined with intensive cognitive and physical rehabilitation on working memory, gait, balance and concomitant changes in the brain of patients diagnosed with multiple sclerosis (MS) was reported by Leonard et al.[6] In this study the controls used a PoNS® device that provided a non-perceivable stimulus. At the end of 14 weeks of treatment, the authors found that there were no significant changes in either group over time on their Beck Depression Inventory, Beck Anxiety Inventory, Multiple Sclerosis Impact Scale and Modified Fatigue Impact Scale scores. The authors also found improvement on most cognitive function in both groups as well as a trend improvement in both groups on their SOT balance test. *It should be noted that although the authors presented this study as a randomized double-blinded controlled trial, it is not clear how randomization was conducted which resulted in an imbalance in potential confounders (see Table 1 in the paper), as well, these potential confounders were also not adjusted for within data analysis, no specific hypothesis with the associated sample size calculation was presented, an unclear patient recruitment and selection method, and multiple comparisons without level 1 error adjustment were reported. In short, potential impact on the outcomes due to bias, chance and confounding cannot be discounted from the observed outcomes on this study*.
- A small (n=122) double-blind randomized controlled trial (level of evidence 1. Appendix 1), investigating whether training using PoNS® at a high-frequency pulse (HFP) is more efficacious than training using a low, but perceivable, frequency pulse (LFP) combined with targeted physical therapy (PT) in patients with balance deficits due to mild-to-moderate traumatic brain injury (M-M TBI), was reported by Ptito et al.[8] in an abstract only format. The designated primary endpoint in this study was an increase in the Sensory Organization Test (SOT) score by > 15 points at 5 weeks (SOT responders), with a secondary endpoint at 2 weeks. The authors reported that 71.4% in the HFP group and 63.5% in the LFP group were SOT responders (P=0.08). Pooling HFP and LFP groups resulted in a responder rate of 67.2%. The mean change in SOT score for the combined group was 18.3 (P < 0.00) from baseline to week 2 and 24.6 (P < 0.00) from baseline to week 5. *Although, given the format of the publication at present as an abstract only, it makes it difficult to appraise the quality of this study, regarding its randomization method, blinding procedure, hypothesis*

and its related sample size, balance in the prognostic factors between HFP and LFP and patient recruitments, certain aspects on the reporting of the outcomes on this study (such as multiple statistical testing outside the designated primary outcome). This study then is likely of low quality. Further, the outcomes demosntrate that there was no difference on the SOT of HFP and LFP.

- In an abstract only format, Skinner and Tyler[10] reported outcomes of their study investigating whether PoNS® at a high-frequency pulse (HFP) was more efficacious than a low-frequency pulse (LFP) in patients with chronic symptoms due to mild-to-moderate traumatic brain injury (M-M TBI). In this study, both groups received targeted physical therapy (PT). It should be noted that this abstract[10] is reporting the same study[13] on which the results were posted on the clinicaltrail.gov websites. Due to the limited information within both papers[10,13], we combined the information available from these two[10,13] papers into this joint appraisal. Forty-four patients with chronic balance deficit due to mmTBI were recruited for this double-blind randomized controlled trial (level of evidence 1. Appendix 1). These patients received 14 weeks of PoNS® treatment, then 12 weeks of normal activity without PoNS® treatment. The primary endpoint was the change in Sensory Organization Test (SOT) composite score, as measured from baseline at the end of week 2 and week 14 visits. The associated sample size was calculated based on these primary outcome points. After following certain assumptions, in order to have a power of 80% with a standard α level of 0.05, the authors calculated that 17 patients were required in each group (for a total of 34). This figure was then legitimately inflated to 22 patients in each group (for a total of 44) in order to account for a 25% patient drop out rate. Randomization was rigourously conducted through the use of a random number generator and was administered by a designated Clinical Monitor. *It should be noted that even though sample size calculations and randomization were done properly, this study only reported on the outcomes of 43 (instead of 44) patients and the planned, one-time interim analysis was not taken into account in their Type I error level. Hence, the effect of randomization was rendered insignificant, while multiple comparisons (which were more evident in the numerous statistical tests reported) were not take into account in the reporting of this study.* The authors reported that the difference in SOT composite scores between the HFP and LFP treatment groups was not statistically significant at week 2, 14, and 26. Further post-hoc analysis of the combined HFP and LFP treatment groups demonstrated statistically significant ($P<0.00$) and clinically meaningful improvements in the SOT composite score from baseline to weeks 2, 14, and 26. The authors concluded that the combination of PoNS® and

targeted PT produced significant improvements in the SOT composite score, which were sustained for at least 12 weeks after intervention was discontinued. *It should be strongly noted that by combining the HFP and LFP group together, the authors changed the nature of the study design from a small double-blind randomized controlled trial (level of evidence 1. Appendix 1) to a small case series (level of evidence 5. Appendix 1). Further, multiple comparisons were evident, based on the number of statistical tests reported. Lastly, the authors were financially involved with Helius Medical Technology®, the manufacturer and distributor of PoNS®, so this conflict of interest needs to be taken into account when interpreting the results of this study*.

- A case report (level of evidence 5. Appendix 1) on the eye movement enhancement in a 66 year-old male with Parkinson's disease as a result of cranial-nerve non-invasive neuromodulation (CN-NINM) intervention with PoNS® was reported by Verbny e al.[11] The CN-NINM intervention used a combination of both physical and cognitive exercises with PoNS®. After a 4-month intervention period, the authors reported gradual enhancement of patient eye movement control in three static nystagmus tests (vertical and horizontal gaze, and spontaneous nystagmus) and three dynamic tests (random saccade, smooth pursuit and optokinetic). *It should be strongly noted that patient selection criteria was not made clear.*
- Verbyny et al.[12] also reported the outcome of cranial-nerve non-invasive neuromodulation (CN-NINM) intervention with PoNS®, for patients with chronic stroke in a small case series (n=5) (level of evidence 5. Appendix 1). After 13 months of intervention, the authors reported that CN-NINM intervention resulted in the gradual enhancement of patient eye movement control in all six eye tests, including static nystagmus tests (vertical and horizontal gaze, and spontaneous nystagmus) and dynamic tests (random saccade, smooth pursuit and optokinetic). *It should be strongly noted that patient selection criteria was not made clear.*
- A small case series (n=6) on the application of PoNS® as treatment for multiple sclerosis patients was reported by Tyler et al.[14] In this study patients were trained in: balance, posture and gait activities, therapeutic exercise for isolated muscle control, transfer training, and relaxation training with concomitant electrical stimulation of the tongue with PoNS®, conducted over a period of 2 weeks, within a laboratory setting. The intervention was customized according to each patient's particular symptoms and tolerance. After these 2 weeks, patients continued to perform these same intervention activities at home for 4 weeks. They then returned to the laboratory for 1 week of training and testing, then performed home training for 4 weeks. This

cycle was repeated for a total of 5 cycles. Trunk Impairment Scale (TIS) was the primary outcome in this study and was measured at baseline, 2, 6, 11, 16, and 21 weeks. There were also numerous secondary outcome measurements proposed. Although there were six patients recruited, only data from four patients were reported at baseline, 2, 6, 11 and 16 week; and only for three patients at 21 week. The absolute TIS difference with baseline value reported was 0.90, 0.57, 1.04, 0.90, 0.49, and 0.32, at 2, 6, 11, 16, 21 and 27 weeks, respectively. The authors stated that the larger the diference between these absolute values, the stronger the effect. *Although there was improvement in the primary outcomes compared to baseline, it should be noted that there was a declining trend of TIS over time; further, the clinical significance of this improvement is unclear. It should also be noted that selection bias cannot be excluded, due to the fact that only the observed results from 4 (out of 6) patients were reported. Further, the potential for financial conflict of interest cannot also be excluded from this study.*

Summary

- At present, there is some low-level, low quality evidence as well as high-level, low quality evidence on the efficacy of PoNS® combined with targeted physiotherapy in treating Mild to Moderate TBI (M-M TBI), cerebellar degeneration, incomplete spinal cord injury, multiple sclerosis, Parkinson's disease and chronic stroke.
- With regard to the efficacy of physiotherapy + PoNS® (c.q. high frequency PoNS® (HFP) vs. low frequency PoNS® (LFP)) in treating M-M TBI, although there are a couple of small randomized controlled trials (level of evidence 1. Appendix 1) published on this topic, it should be noted that bias, chance and the impact of confounders cannot be excluded from the observed outcomes; potential conflicts of interest also cannot be excluded and perhaps most importantly, the fact that there was no difference between HFP and LFP with regard to the reported Sensory Organization Test (SOT) outcome scores, suggest that targeted physical therapy as an intervention may be the variable responsible for the difference between baseline and follow-up results. Thus, these observed outcomes also suggest a potential for the placebo effect in the use of PoNS®.

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Appendix 1

WorkSafeBC - Evidence-Based Practice Group Levels of Evidence (adapted from 1,2,3,4)

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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