Music medicine to improve the tolerability of onabotulinumtoxinA injections for chronic migraine: an open-label prospective cohort study

Jason Ray, Subahari Raviskanthan

ABSTRACT

Introduction OnabotulinumtoxinA for migraine involves 31 injected repeated every 12 weeks. Tolerability is a significant factor impacting discontinuation. Music medicine has not been studied previously as an intervention to improve the tolerability of injections.

Methodology A single-centre prospective cohort study was undertaken. Following baseline, patients had music played during the procedure. Change in Visual Analogue Score (VAS) was assessed as the primary outcome.

Results Over 6 months, 50 patients were recruited with a median age of 42, and median duration of therapy of 13.5 months. ‘Quiet calm classical music’ was associated with a significant reduction in VAS (z = −4.7, p < 0.001). Duration of therapy, disease state or headache frequency had no correlation with change in VAS.

Conclusion Music medicine is associated with a significant reduction in the procedural pain of onabotulinumtoxinA injections in prospective study. Further study is required to explore other modifiable factors to improve patient experience.

INTRODUCTION

OnabotulinumtoxinA (BoT-A) is an effective preventative treatment for chronic migraine that involves 31 local injections administered at 12-weekly intervals following the PREEMPT protocol. Despite the efficacy of BoT-A, the discomfort of the injections is a significant factor in the tolerability of treatment, and is the primary reason for discontinuation in 1.3% of patients. Currently, there is limited data addressing the tolerability of BoT-A in treatment of chronic migraine.

Music medicine is the provision of pre-recorded music by a healthcare professional, and has been studied as an adjunct in pain management in multiple other settings. It is distinct from music therapy, which is the clinical utilisation of music in a therapeutic encounter by an appropriately trained professional. The use of music medicine on the experience of pain during BoT-A injections for chronic migraine has not been previously investigated.

METHODOLOGY

A single-centre prospective cohort study was performed in the tertiary headache clinic of Alfred Health, Melbourne, Australia. Patients with chronic migraine per International Classification of Headache Disorders 3rd edition criteria that were receiving BoT-A injections by the PREEMPT protocol following local regulatory guidelines were enrolled in the study. Patients were excluded from the study if they had not received BoT-A injections prior to the first visit.

Patients were recruited from September 2022 to February 2023. Following a baseline visit and injection, a ‘quiet calm classical’ playlist (online supplemental appendix 1) was played on a portable speaker in the corner of the room during the next clinical visit. Two injectors participated in the study, and there was no variability with injector at each appointment. There was no variability with injector at each appointment. Change in 11-point Visual Analogue Scale (VAS) of injection was chosen as the primary endpoint. Patients were asked ‘on a scale of 1–10, how painful was the injection?’. Monthly headache days (MHD) were measured by patient report from headache diary in the month prior to each appointment (ie, week 9–12 after previous BoT-A administration). Disease state on the day of the injection was recorded as either ictal or interictal.

Statistical analysis was performed using SPSS V.28.0. Population characteristics were summarised with descriptive statistics. Longitudinal change was assessed with Wilcoxon signed rank test for non-normally distributed data. Spearman’s rank-order correlation was

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used to assess correlation. Tests results were considered significant when $p<0.05$.

**RESULTS**

A total of 50 patients were enrolled in the study over a 6-month period. Population characteristics are summarised in Table 1. The population had a median age of 42 (SD 15.1), had been on treatment for a median of 13.5 months (IQR 20), and had a baseline MHD frequency of 8 days (IQR 12).

Playing ‘quiet calm classical music’ during the injection was associated with a significant reduction in VAS ($z=-4.7$, $p<0.001$), with a median reduction by 1 (IQR 2.0). Over the 3-month follow-up period, there was also a significant reduction in MHD ($z=-2.9$, $p=0.004$). A Spearman’s rank-order correlation found no correlation between change in VAS and MHD ($r=-0.09$, $p=0.535$), or with change in VAS and duration of therapy with BoT-A ($r=-0.270$, $p=0.058$). The individual percentage change in VAS is represented in Figure 1.

The impact of disease state on the day of injection on VAS was also investigated as a possible confounder. A Kruskal-Wallis H test showed there was no significant difference in pain score between patients who had both injections in an interictal state, and those who had either injection while experiencing a headache ($p=0.322$).

**DISCUSSION**

This is the first prospective study to evaluate the use of music as a therapeutic technique to lessen the discomfort of BoT-A in chronic migraine, and has shown that playing ‘quiet calm classical music’ significantly reduces the pain of injections following the PREEMPT protocol, improving the tolerability of the procedure. This relationship appears independent of duration of therapy, ictal/interictal disease state or change in headache frequency.

Music medicine is effective at modulating pain in experimental conditions, however, the underlying mechanism remains uncertain, with hypotheses including cognitive and emotional modulation. Listening to ‘relaxing’ music has been shown to modulate the hypothalamic-pituitary-adrenal axis and modulate stress in several studies. Physiological effects of music have also been noted, with an improvement in blood pressure, respiration rate, heart rate and cortisol levels. In a 2016 meta-analysis of the effects of music on pain, Lee reported a reduction of VAS with a similar magnitude of effect of 1.13 (95% CI $-1.44$ to $-0.82$, $p<0.00001$) on a 0–10 VAS. There remains significant variability in the literature on the reporting of the impact of different music genre, with limited head-to-head comparisons. Overall, studies show stronger benefit in classical music, however, Trappe reported that particular songs appeared more beneficial in different clinical settings.

Ayinde and colleagues have previously studied other methods to reduce the discomfort of intramuscular injections, that have not previously been investigated in migraine. In a 2021 systematic review and meta-analysis, they reported improvement in pain post intramuscular injection with applying manual pressure or skin tapping, but variable evidence regarding the speed of injection.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Population demographics at baseline and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, n=50</td>
</tr>
<tr>
<td>Age, Median (IQR)</td>
<td>42 (20)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>42 (84.0)</td>
</tr>
<tr>
<td>Duration of BoT-A, Median (IQR)</td>
<td>13.5 (27)</td>
</tr>
<tr>
<td>VAS, Median (IQR)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>MHD, Median (IQR)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>BoT-A, onabotulinumtoxinA; MHD, monthly headache days; VAS, Visual Analogue Score.</td>
<td></td>
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</tbody>
</table>

![Percentage change in VAS](image1.png)

**Figure 1** Percentage reduction in VAS over study period with classical music. VAS, Visual Analogue Score.
These techniques were explored in the setting of higher volume injections in the gluteal or deltoid region and typically did not involve multiple injections in the same session, so the applicability in PREEMPT BoT-A requires further evaluation. Evaluation of low-risk techniques such as music medicine and manual pressure is valuable given the ease of implementation and beneficial impact on patient experience.

There are some limitations to this study. First, as a non-blinded study, an assessment of causation is limited. The study was designed as a prospective, single group cohort with paired-sample analysis. The fact that the study occurred at a single centre, and with a relatively small cohort, also represents a further limitation which limits generalisability. While this design is methodologically sound and controls for co-confounders such as differential experience and report of pain, it is possible that successive exposure to BoT-A reduces peripheral sensitisation and thus the perception of pain irrespective of other factors. No association between duration of BoT-A therapy and change in VAS was observed, which suggests that this was not a significant factor. The genre of music was the same for all patients enrolled, however, potentially other genres of music, or allowing the patient to choose their genre or the individual songs played may yield different results and could be an area for further study.

CONCLUSION
Music medicine with ‘quiet calm classical music’ is associated with a significant reduction in discomfort during BoT-A injections for chronic migraine. Further study is now required to determine if reduction in VAS is associated with improved tolerability and reduced discontinuation of the procedure.

Contributors JR and SR contributed equally to study conception, data acquisition, manuscript preparation and revision.

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Competing interests JR has received funding for educational presentations Allergan, Novartis and has served on medical advisory boards for Pfizer, Viatris and Lilly. SR has no conflict of interest to declare.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Alfred Health Office of Ethics & Research Governance HREC 516/22. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The dataset for this manuscript will be made available upon reasonable request subject to appropriate ethics submission and approval.

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REFERENCES
## Appendix 1: Playlist

**Calming Classical Mix**

<table>
<thead>
<tr>
<th>Title</th>
<th>Artist</th>
<th>Album</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clair de Lune, L. 32</td>
<td>Claude Debussy, Martin Jones</td>
<td>Debussy: Clair De Lune and Other Piano Favourites</td>
</tr>
<tr>
<td>Hymn</td>
<td>Karl Jenkins</td>
<td>Karl Jenkins: Piano</td>
</tr>
<tr>
<td>Bag End</td>
<td>Howard Shore</td>
<td>The lord of the Rings: the fellowship of the ring – the complete recordings</td>
</tr>
<tr>
<td>The Lamb</td>
<td>John Tavener, 12 Ensemble</td>
<td>Taverner: The Lamb</td>
</tr>
<tr>
<td>Variations on the Kanon</td>
<td>George Winston</td>
<td>December</td>
</tr>
<tr>
<td>Kinderszenen, Op. 15: No. 1, Von fremden Ländern und Menschen</td>
<td>Robert Schumann, Vladimir Horowitz</td>
<td>Schumann: Kinderszenen; Abarasque; Fantasie; Träumerei</td>
</tr>
<tr>
<td>Ave Maria</td>
<td>Johann Sebastian Bach, Charles Gounod, Kian Soltani, Aaron Pilsan</td>
<td>J.S. Bach, Gounod: Ave Maria</td>
</tr>
<tr>
<td>Fracture</td>
<td>Stephan Moccio</td>
<td>Tales of Solace</td>
</tr>
<tr>
<td>The Lord Bless you and Keep You</td>
<td>John Rutter, The Cambridge Singers</td>
<td>The Ultimate Collection</td>
</tr>
<tr>
<td>Still</td>
<td>Ola Gjeilo</td>
<td>Night</td>
</tr>
<tr>
<td>Very Old Friends</td>
<td>Howard Shore</td>
<td>The lord of the Rings: the fellowship of the ring – the complete recordings</td>
</tr>
<tr>
<td>Dawn – From “Pride &amp; Prejudice” Soundtrack</td>
<td>Jean-Yves Thivaudet</td>
<td>Pride and Prejudice OST</td>
</tr>
<tr>
<td>In the Bleak Midwinter (Arr. Gjeilo)</td>
<td>Gustav Holst, Voces8</td>
<td>Winter</td>
</tr>
<tr>
<td>Tomorrow's Song</td>
<td>O$lfur Arnalds, Lavinia Meijer</td>
<td>The Glass Effect</td>
</tr>
<tr>
<td>Thanksgiving</td>
<td>George Winston</td>
<td>December</td>
</tr>
<tr>
<td>Lullaby (Guten Abend, gut’ Nacht)</td>
<td>Johannes Bramh, Fabian Müller</td>
<td>Lullaby (Guten Abend, gut’ Nacht)</td>
</tr>
<tr>
<td>Concertino bianco: 1. Con intenerimento</td>
<td>Georgs Pelècis, Johannes Fritzsch, Tamara Anna Cisłowska</td>
<td>Into Silence</td>
</tr>
<tr>
<td>Ave Maria (Arr. Vikingur Ólafsson) – Upright piano</td>
<td>Sigvaldi Kaldalòns, Vikingur Ólafsson</td>
<td>Kaldalòns: Ave Maria</td>
</tr>
<tr>
<td>My Father’s Favourite</td>
<td>Patrick Doyle, Tony Hymas, Robert Ziegler</td>
<td>Sense &amp; Sensibility – original motion picture soundtrack</td>
</tr>
<tr>
<td>Nuch loved</td>
<td>Rachel portman</td>
<td>The lord of the Rings: the fellowship of the ring – the complete recordings</td>
</tr>
<tr>
<td>The Shire</td>
<td>Howard Shore</td>
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<tr>
<td>Robin’s Cello</td>
<td>Phoria</td>
<td>Caught a Black Rabbit</td>
</tr>
<tr>
<td>Ave Maris Stell</td>
<td>Edward Grieg, Gabrieli, Paul McCresch</td>
<td>An evening of classical: grieg</td>
</tr>
<tr>
<td>The hours: an unwelcome friend (from “the hours”)</td>
<td>Philip Glass, Nicolas Horvath</td>
<td>Philip Glass: Glasssworlds, Vol. 4 – on love</td>
</tr>
<tr>
<td>Music for growing flower – Pt. 4</td>
<td>Erland Cooper</td>
<td>Music for growing flowers</td>
</tr>
<tr>
<td>Joy</td>
<td>George Winston</td>
<td>December</td>
</tr>
<tr>
<td>Elizabethan Masque</td>
<td>Frederico Bayco, Pro arte orchestra, George Weldone</td>
<td>British Composers: Best of british</td>
</tr>
<tr>
<td>Anne’s Theme</td>
<td>Hagood Hardy</td>
<td>All my best</td>
</tr>
<tr>
<td>Days of Beauty</td>
<td>Ola Gjeilo, The choir of royal Holloway, 12 Ensemble</td>
<td>Winter Songs</td>
</tr>
<tr>
<td>Frost</td>
<td>Gabriel Ólafsson</td>
<td>Frost</td>
</tr>
<tr>
<td>...And at the hour of death</td>
<td>Vikingur Ólafsson</td>
<td>Bach Reworks (Pt. 1)</td>
</tr>
<tr>
<td>The passing of the Elves</td>
<td>Howard Shore</td>
<td>The lord of the Rings: the fellowship of the ring – the complete recordings</td>
</tr>
<tr>
<td>And so the story began</td>
<td>Jef Martens</td>
<td>Evenings on Instagram, Pt. I</td>
</tr>
<tr>
<td>Nimrod from enigma variations</td>
<td>Edward Elgar, Royal Philharmonic Orchestra, Philip Ellis</td>
<td>Last night of the proms</td>
</tr>
<tr>
<td>Romantic flight</td>
<td>John Powell</td>
<td>How to train your dragon (Music from the motion picture)</td>
</tr>
<tr>
<td>Piece</td>
<td>Performer/Artist/Ensemble</td>
<td>Album/Work Description</td>
</tr>
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</tr>
<tr>
<td>L’Arlésienne Suite No. 2: Menuet</td>
<td>Georges Bizet, Orchestre Symphonique de Montréal, Charles Dutoit</td>
<td>Bizet: Carmen Suits 1 &amp; 2; L’Arlesienne Suites 1 &amp; 2</td>
</tr>
<tr>
<td>The arts and the Hours</td>
<td>Jean-Philippe Rameau, Vikingur Ólafsson</td>
<td>Rameau, Ólafsson: The arts and the hours</td>
</tr>
<tr>
<td>Merry Christmas Mr. Lawrence</td>
<td>Jess Gillm, Oschar Holch, Rowena Calvert, Sma Becker</td>
<td>Merry Christmas Mr. Lawrence</td>
</tr>
<tr>
<td>Pachelbel’s Canon in D</td>
<td>Pat Richardson</td>
<td>Pachelbel’s Canon in D</td>
</tr>
<tr>
<td>Northern Lights</td>
<td>Ola Gjeilo, Voces8</td>
<td>Ola Gjeilo</td>
</tr>
<tr>
<td>Ashokan Farewell</td>
<td>Jay Ungar, Nashville Chamber Orchestra, Paul Gambill</td>
<td>Harvest Home</td>
</tr>
<tr>
<td>Rivendell</td>
<td>Howard Shore</td>
<td>The lord of the Rings: the fellowship of the ring – the complete recordings</td>
</tr>
<tr>
<td>5 Anniversaries: No. 5 For Susanna Kyle</td>
<td>Leonard Bernstein, Warren Lee</td>
<td>Touches &amp; Traces</td>
</tr>
<tr>
<td>Greensleeves</td>
<td>David Nevue</td>
<td>Sweet Dreams &amp; Starlight</td>
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