BOWEL CARE AND CARDIOVASCULAR FUNCTION AFTER SPINAL CORD INJURY

This description of the study protocol and statistical analysis plan is taken from the published article containing all study details:

V-E.M. Lucci, M.S. McGrath, J.A. Inskip, S. Sarveswaran, R. Willms, **V.E. Claydon** (2020) Clinical recommendations for use of lidocaine lubricant during bowel care after spinal cord injury prolong care routines and worsen autonomic dysreflexia: results from a randomised clinical trial. *Spinal Cord,* **58**: 430-440. (www.nature.com/articles/s41393-019-0381-2)

MATERIALS AND METHODS

Ethical Approval

This study was approved by the Department of Research Ethics at Simon Fraser University and conforms to the principles outlined in the Declaration of Helsinki [25]. Participants provided written informed consent and the trial was registered (Clinical.Tials.gov #NCT01567605).

Participants

Participants were recruited using a multi-method approach. Print advertisements were circulated through our community partner, Spinal Cord Injury British Columbia, via their quarterly publication, *The Spin*, and online advertisements were posted through our institutional website (www.icord.org).

Eligible participants were individuals aged >18 years of age with chronic (>1 year) traumatic high level (T6 or above) SCI, who had an established bowel care routine, and a prior history of AD. Individuals were excluded if they had a medical/psychiatric condition or substance abuse disorder, used a ventilator, had a colostomy, or did not perform regular bowel care for any reason. Additional exclusion criteria included skin breakdown in the areas receiving pressure during the bowel program, inability to communicate in English, use of medicines containing lidocaine, allergy to lidocaine, and pregnancy.

Our primary outcome measure was the difference in systolic arterial pressure between the placebo and lidocaine conditions. We determined a meaningful difference to detect in blood pressure between the two study arms of 10mmHg (based on previous unpublished observations from our lab). With a power of 0.8 and alpha of 0.05, we determined a sample size of 13 individuals would be necessary to ensure statistical confidence in our ability to detect differences in this primary outcome measure.

Experimental Procedure

We conducted a registered double-blind placebo-controlled crossover clinical trial where participants were randomised to a series of two treatments: lidocaine lubricant (Xylocaine 2%) and standard lubricant (KY Jelly; placebo) on two consecutive at-home visits (**Figure 1**). The sequence of conditions was determined by random draw, using a complete randomised design, by a researcher external to the research team; seven participants were randomised to the lidocaine arm of the study first, and six to the placebo arm of the study first. Testing took place between August 2016 and October 2018.

Prior to the first visit, participants completed a questionnaire about their bowel management and general bowel continence [5]. On each visit, participants were fitted with a standard three-lead electrocardiogram (ECG; lead II) and a non-invasive beat-to-beat finger blood pressure monitor (Finometer Midi, Finapres Medical Systems [FMS], Amsterdam, Netherlands). After a 10-minute baseline recording (sampling rate 200Hz) participants inserted 5mL of lubricant into the rectum using a specialised device (Lube Launcher XL, CleanStream, Huntington Beach, USA) to ensure that a minimum amount of lubricant was administered. Following insertion of the lubricant, participants waited 5-min before starting bowel care (to allow for mucosal absorption of lidocaine, which has a typical onset of action of 3-5 minutes). Participants were then provided with an additional 15mL of lubricant and asked to perform their bowel care routine as

usual, replacing their normal lubricant with the lubricant provided for that day. The maximum recommended dosage of lidocaine is 600mg/12 hour. The dosage provided (20ml of 2% lidocaine) is equivalent to 400mg. The 20ml volume was determined based on discussion with bowel care providers and individuals with SCI concerning their typical lubricant needs. This dosing strategy is in line with other similar studies. Given the typical half-life of lidocaine (1.5-2 hours) we are confident there was optimal dosing throughout the duration of bowel care.

Five minutes after insertion of the test lubricant, a timer was started and the participant commenced their usual care routine. Bowel care routines were not standardised because the primary interest was to investigate the real-world feasibility and impact of this clinical recommendation in a community setting with usual participant care routines. When the participant signalled the end of their care routine (defined as the time when bowel evacuation was completed, prior to cleaning), the timer was stopped, and the bowel care duration noted. The cardiovascular monitoring equipment was then removed. Participants then completed a questionnaire specific to their bowel care on that day, reporting the method of bowel care employed as well as the severity of cardiovascular symptoms experienced [5]. Self-reported symptoms of AD were determined as described previously [5]. Two participants chose not to complete the post-bowel care questionnaire.

Autonomic dysfunction

Severity of autonomic dysfunction was determined through spectral analyses of low-frequency systolic arterial pressure variability (LF SAP). LF SAP oscillations (~0.1Hz) reflect sympathetic control of the vasculature, and thus indicate the presence or absence of autonomic cardiovascular control following SCI [26]. Participants with LF SAP lower than 3.75mmHg^2 were determined to have autonomically-complete injuries.

Cardiac rate and rhythm analyses

Electrocardiogram data were visually inspected offline after completion of the study. The number of beats that met criteria for bradycardia (<60bpm) and tachycardia (>100bpm) was determined during baseline and bowel care, and expressed as a percentage of the total number of beats in the corresponding phase. In addition, each beat was classified as either sinus rhythm, or not, and any arrhythmia or conduction abnormalities noted.

Data analyses

Beat-to-beat systolic (SAP) and diastolic (DAP) arterial pressures were extracted throughout the testing period. Mean arterial pressure (MAP) was calculated as DAP + 1/3 x (SAP-DAP). Heart rate was determined from the R-R interval of the ECG. Stroke volume (SV) and cardiac output (Q) were determined using Modelflow [27,28], and total peripheral resistance (TPR) calculated as MAP / Q. Data were collected at a sampling frequency of 200 Hz and averaged over 5 successive beats. All parameters were extracted for the entire duration of baseline and bowel care, as well as for only the first 25 minutes of bowel care. Maximal responses were also determined during bowel care regardless of the time at which they occurred (Parameter$_{max}$). AD was defined as an increase in SAP$_{max}$ of at least 20mmHg [29] compared to baseline. The overall burden of AD was determined from the area under the SAP curve (the product of SAP and heart beat).

Statistical analyses

Data processing was performed using R (Version 3.3.3) and RStudio (Version 1.1.453). Statistical analyses were performed using Sigmaplot 14 (Systat Software Inc., San Jose, CA). Data were tested for normality and parametric or non-parametric assumptions were used as appropriate. Comparisons of cardiovascular outcomes and symptoms between conditions (lidocaine and placebo) and test phases (baseline and during bowel care) were performed using two-way repeated measures ANOVA. Spearman rank correlations and

linear regressions were used to assess relationships between variables. Fisher's exact test was used to evaluate differences in proportions of responses between test conditions. Student t tests were used to compare responses between placebo and lidocaine conditions (e.g. time to complete bowel care). Statistical significance was assumed at $p<0.05$. Where appropriate, data are represented as mean ± standard error, unless otherwise stated. Researchers, participants, care providers, and those analysing the data were blinded to the test condition. Researchers were unblinded just prior to statistical analyses.