Research Article

Intravesical hyaluronic acid with chondroitin sulphate to prevent urinary tract infection after spinal cord injury

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Context/Objective: Prevention of urinary tract infection (UTI) after spinal cord injury is an important goal. Intravesical hyaluronic acid with chondroitin sulphate (HA+CS) has been effective in preventing UTI in other settings. We aimed to demonstrate safety and feasibility of a standard treatment course of 7 intravesical HA+CS instillations over 12 weeks, in patients with acute (Arm A) and chronic (Arm B) spinal cord injury (SCI).
Design: Follow-up of adverse events, quality of life bladder management difficulty (BMD) and bladder complication (BC) *T*-scores at baseline (Arm B only), 12 and 24 weeks, and symptomatic urinary tract infection (UTI).
Results: Of 33 and 14 individuals screened, 2 and 8 participants were recruited to the study for Arm A and Arm B respectively. Of the 10 participants, 8 completed all 7 instillations. HA+CS commonly caused cloudy urine with urinary sediment which was mild and short-lived. In Arm B, a mean reduction in BMD and BC T-scores was observed from baseline (57.3 and 54.4 respectively), of 6.8 and 4.3 at 12 weeks and 1.6 and 2.8 at 24 weeks, respectively. Four participants with a history of frequent UTI in the prior 12 months did not have UTI in the 24 weeks of the study.
Conclusions: HA+CS was well tolerated. Recruitment was more difficult in early acute SCI; participants with chronic SCI were highly motivated to reduce UTI and manage self-administration without difficulty. Larger case–control or randomized controlled trials in patients with neurogenic bladder from SCI are warranted.
Trial registration: ClinicalTrials.gov identifier: NCT03945110.

Keywords: Urinary tract infection, UTI, Spinal cord injury, Hyaluronic acid, Chondroitin sulphate

Introduction

Traumatic spinal cord injury (SCI) presents significant impacts and considerable costs to affected individuals and society. In addition to paralysis and sensation loss, the effects of SCI on the urinary bladder are immediate, with altered voiding dynamics and pathogenic mechanisms including bladder ischemia, hypoperfusion, abnormal microbiological architecture, damage to the urothelial barrier and dysregulated inflammatory responses, rendering patients susceptible to urinary tract infection (UTI).[1] Acute bladder

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management requires urethral indwelling catheterization (IDC), which further increases UTI susceptibility. Following SCI, genitourinary diseases including UTI result in significant long-term morbidity are the leading cause of re-hospitalization,[2–5] and the second leading cause of death.[6] Individuals with chronic SCI and neurogenic bladder require ongoing IDC or intermittent catheterization (IC), which further increases the risks of mucosal irritation, catheter cystitis and recurrent UTI. People with chronic SCI experience a mean 2.14 UTIs per year,[7–9] though up to 19% have >6 infections per year.[8] There are few prophylactic measures with strong evidence-based efficacy for people with neurogenic bladder,[10] and antibiotic prophylaxis is not generally advisable, since this may promote antibiotic resistance.[11]

Our recent audit of acute SCI bladder management and UTI in Western Australia (WA), 2015–2017, found that for patients with ≥1 UTIs ($n = 43/70$), a more prolonged duration of initial IDC was associated with shorter time to first UTI, which in turn was associated with an increased frequency of subsequent UTI.[12] These findings indicate that prevention of UTI during early acute SCI may reduce subsequent rates of infection.

Restoring the integrity of the urothelium has been an effective strategy to reduce recurrent UTI in neurologically intact populations.[13] The healthy urothelium is coated with a film consisting of glycosaminoglycans (GAGs), highly hydrophilic molecules that create a protective barrier. Animal models have demonstrated disruption of this layer following SCI, exposing the urothelium to toxins in the urine, leading to increased UTIs. Infection further damages the GAG layer, promoting progressive damage and recurrent infection.[14] Studies over the last 20 years have explored ways to restore the GAG layer, including introducing hyaluronic acid (HA) and chondroitin sulphate (CS) intravesically via a catheter.[15] HA and/or CS bladder instillations are safe and produced promising results for recurrent UTI in the general population.[13] For individuals hospitalized with metastatic spinal cord compression requiring IDC, intravesical HA instillation was effective in preventing UTI.[16] There is very limited research into the effectiveness of intravesical GAGs at preventing UTI in people with neurogenic bladder, including those with SCI,[17,18] and none have examined these instillations in the early acute phase post-injury. The non-antibiotic prevention approach has minimal administrative burden for individuals who routinely require catheterization. We, therefore, conducted an exploratory study primarily on the feasibility and tolerability of intravesical HA + CS in people with SCI. Measures to prevent UTI need to be tested in both acute and chronic SCI as there may be differences between the two groups in the efficacy and implementation of an intervention.

Objectives

- Acute Arm (Arm A): To examine the safety and feasibility of 7 bladder instillations of HA and CS (HA + CS) over 12 weeks, commencing within 10 days of traumatic SCI (before the onset of UTI)
- Chronic Arm (Arm B): To examine the safety and feasibility of 7 bladder instillations of HA + CS over 12 weeks, performed by patients with chronic SCI (rehabilitation phase or community) and a history of recurrent UTI.

Materials and methods

Trial design and setting

This is an exploratory study involving patients with acute and chronic SCI. All Participants followed Western Australian (WA) standard care pathways in relation to bladder management following SCI.

The trial was conducted across the two main hospital sites managing SCI in WA: Royal Perth Hospital (RPH, "Surgical Hospital") and the State Rehabilitation Service at Fiona Stanley Hospital (FSH, "Rehabilitation Hospital"), and a private urology clinic ("Clinic"), over a 12-month period.

Eligibility and recruitment

Inclusion and exclusion criteria for Arm A and B are displayed in Table 1. Figure 1 summarizes screening and enrolment in Arm A and Arm B. For Arm A, of 33 potential patients at screening, only four ultimately met eligibility criteria and two completed the seven HA + CS instillations. The main exclusions were >70 years of age ($n = 9$) and spontaneous voiding of urine prior to day 10 ($n = 6$).

Fourteen individuals from the community were screened and eight participants were recruited to Arm B. Reasons for exclusion were; not sudden onset SCI ($n = 3$), remote location so unable to attend clinic ($n = 1$), no history of recurrent UTI ($n = 2$). Six participants completed all installations to be fully analyzed. One participant (participant 9) completed six instillations. The final instillation for participant 9 was not given due to an inability to attend the clinic. One participant (participant 10) received a single instillation in hospital but due to COVID-19 restrictions he couldn't attend clinic for further instillations, and follow-up was limited to 46 days (see Fig. 1).

Intervention

The 12-week protocol consisted of seven bladder instillations of HA + CS (iAluRil®) which were administered according to the product insert at weeks 1, 2, 3, 4, 6, 8 and 12 through a urinary catheter using 50 mL pre-filled syringes containing a sterile solution of sodium hyaluronate (1.6% 800 mg/50 mL) and sodium chondroitin sulphate (2%–1 g/50 mL). iAluRil® syringes are registered on the Australian Register of Therapeutics Goods as a class III medical device.

Arm A procedure

Instillations were administered by attending nurses who were trained by study author GKK, who has extensive SCI nursing experience. Following complete bladder emptying, HA + CS was instilled at room temperature slowly (over 5 min) via the catheter which was then clamped for a minimum 30 min. Standard observations were recorded before and after instillation. Participants were monitored for adverse events, including signs of AD, a potentially life-threatening condition occurring in some patients with injuries at or above neurological level T7 and is characterized by a sudden increase in blood pressure and may be triggered in susceptible individuals by instilling a fluid into the bladder and/or catheter clamping. We administered intravesical instillations slowly at room-temperature to minimizes this risk.

Arm B procedure

Instillations were administered by attending nurses per Arm A for inpatients who were not performing self-intermittent catheterization (self-IC). All other participants administered HA + CS themselves at an outpatient clinic supervised by spinal urology nurses, who provided instruction and assistance, and ensured good technique with full emptying of the bladder via self-IC. Participants remained in clinic for 30 min after HA + CS instillation for the monitoring of adverse events. Pre- and post- instillation observations were recorded.

Data collection

All participants were followed for 24 weeks, to allow surveillance for outcomes up to 12 weeks after the final HA + CS instillation. The following data were collected from medical records for inpatients and from a Log Book* provided to all Arm B participants and to Arm A participants discharged before 24 weeks:

1. Demographics, medical history, injury details and neurological status
2. Bladder management methods and durations
3. Concurrent medications, illnesses and urological complications
4. Episodes of symptomatic UTI, defined according to guidelines of the Infectious Diseases Society of America as bacteriuria ($\geq 10^4$ CFU/mL of ≥ 1 bacterial species in catheter or midstream urine samples), plus symptomatology with no other identifiable cause.[19]
5. Renal ultrasound and urodynamic assessment results (conducted ~12 weeks post-SCI as part of standard care for acute patients).

Two validated bladder-related quality of life surveys (SCI-QoL 'Bladder Management Difficulties SF8a' and 'Bladder Complications'),[20,21] were conducted with each participant at baseline (Arm B only), 12 and 24 weeks post-enrolment. The "Bladder Management Difficulties" (BMD) survey involves eight questions related to how bladder management interferes with a person's life. Each question is graded 1 (not at all) to 5 (very much), with the raw score converted to a T-score ranging from 40.9 to 81.6. The "Bladder Complications" (BC) survey involves 5 questions related to the interference of UTI on quality of life and bladder issues on sex life, rated 1 (not at all) to 5 (very much), converted to a T-score ranging from 39.7 to 76.7. *T*-score of 50 reflects the mean score from a calibration study in the SCI population, with each difference of 10 points representing one standard deviation. Higher scores indicate increased difficulties or complications. A short survey on satisfaction and

Table 1 Inclusion and exclusion criteria for Arms A and B of the study.

Inclusion criteria	Arm A	Arm B
Age 18–70 years	Yes	Yes
Traumatic SCI	Yes	Yes
Atraumatic sudden onset SCI	No	Yes
Within 10 days post-SCI	Yes	No
History of recurrent UTI	No	Yes
Exclusion criteria		
Admission to hospital outside Western Australia	Yes	No
Inability to commence HA + CS Within 10 days of SCI	Yes	No
Spontaneous voiding	Yes	Yes
Bladder/urethral trauma on Admission	Yes	Yes
Bladder cancer/other bladder Pathology	Yes	Yes
Known hypersensitivity to HA or CS	Yes	Yes
UTI before commencing Study intervention	Yes	No
Current pregnancy	Yes	Yes
History of neurological disorder	Yes	Yes
Inability to provide consent	Yes	Yes
History of autonomic Dysreflexia with urological procedures	No	Yes

CS = chrondroitin sulphate, HA = hyaluronic acid, SCI = spinal cord injury, UTI = urinary tract infection.

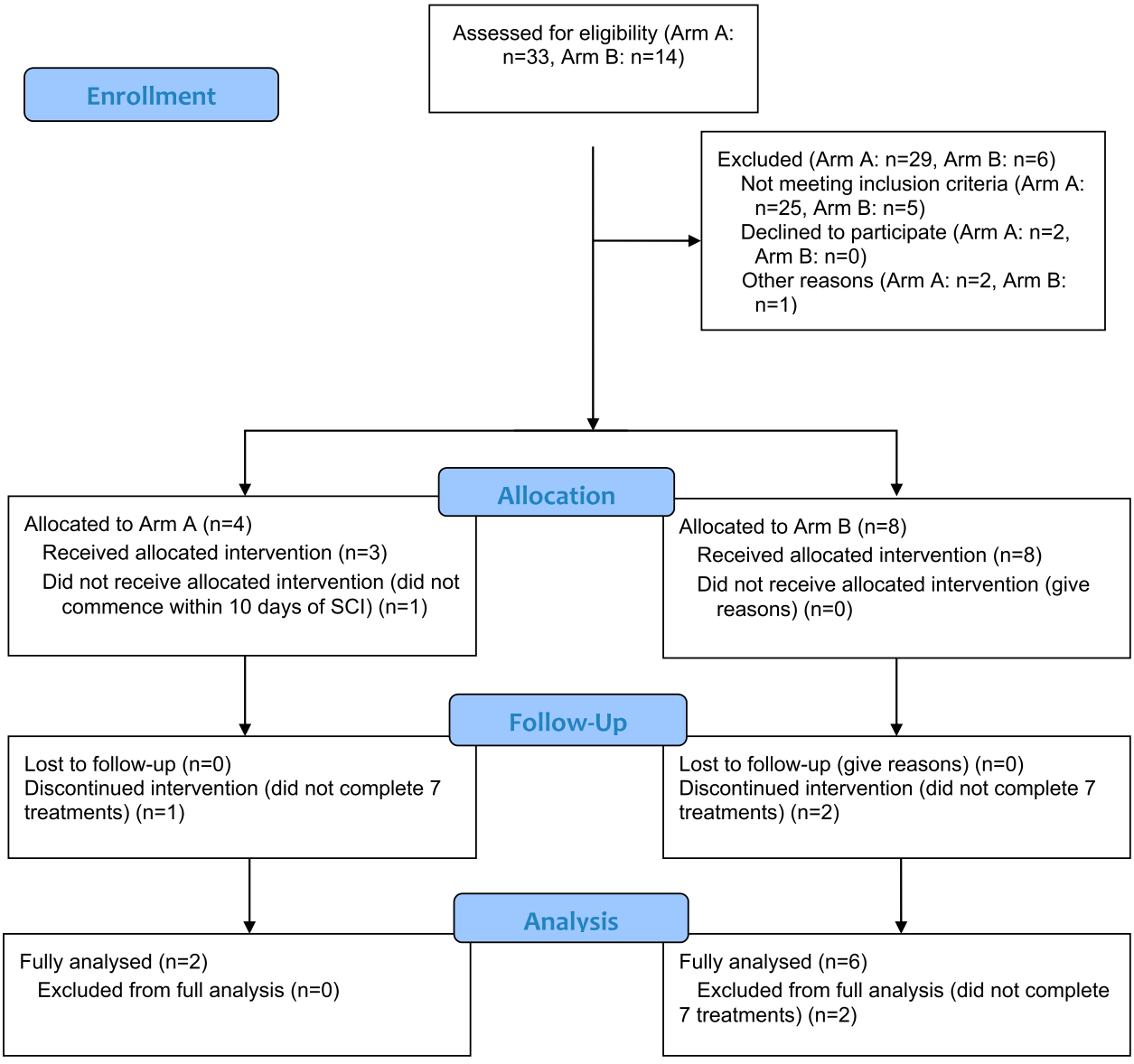

Figure 1 Consort study diagram.

ease of instillation was also conducted at 24 weeks. Arm B participants were questioned about UTIs (requiring antibiotics) during the 12 months before enrolment.

Statement of ethics

The study was conducted with informed patient consent, received ethical approval from The South Metropolitan Health Service Human Research Ethics Committee (RGS-2994), and is registered on ClinicalTrials.gov (NCT03945110) and the Australian and New Zealand Clinical Trials Registry.

Results

Arm A

Participant 1 was a 32-year-old male with injury at neurological level C4 who had an IDC for 65 days, followed by staff-IC for 66 days, and at study completion bladder was managed with IDC awaiting final management via suprapubic catheter (SPC). His Surgical Hospital stay was 37 days and Rehabilitation Hospital stay 94 days. He had two UTIs. BMD T-scores were 53.2 at 12 weeks and 49.8 at 24 weeks. BC *T*-scores were 55.5 at 12 weeks and 45.8 at 24 weeks. Participant 2 was an 18-year-old male with injury at neurological level T5 who had IDC for 21 days followed by self-IC. His Surgical Hospital stay was 17 days and Rehabilitation Hospital stay 56 days. He had no UTIs. BMD *T*-scores were 53.2 at 12 weeks and 54.8 at 24 weeks. BC T-scores were 45.8 at 12 weeks and 45.8 at 24 weeks (see Table 2). Neither participant found instillations bothersome and both were glad to have participated in the study.

Table 2 Demographics and outcomes of participants in Arm A (acute spinal cord injury [SCI]), Arm B (chronic SCI), indicating ISNSCI spinal cord level (Le), Complete SCI (Co), Years since injury (Ye), Bladder management during the treatment phase (BM; IDC = indwelling catheter, IC = intermittent catheter), urinary tract infection (UTI) in the 12 months before study, UTI during the study, SCI-QoL Bladder Management Difficulty (BMD) and Bladder Complication (BC) T-scores at baseline (Ba), 12 and 24 weeks, and median/geometric mean Arm A, Arm B, Arm A + B for Age, Ye, UTI 12M, UTI study, BMD, BC.

	Sex	Age	Le	Co	Ye	BM	UTI 12M	UTI study	BMD Ba	BMD 12W	BMD 24W	BC Ba	BC 12W	BC 24W
Arm A														
1	M	32	C4	Y	0	IDC	N/A	2	N/A	53.2	49.8	N/A	55.5	45.8
2	M	19	T5	Y	0	IDC/IC	N/A	0	N/A	53.2	54.8	N/A	45.8	45.8
Median/Mean		25.5/24.6			0/0			1/1		53.2/53.2	52.3/52.3		50.6/50.6	45.8/45.8
Arm B														
3	F	42	T5	Y	22	IC	1–3	1	58.9	51.8	53.2	45.8	58.6	45.8
4	F	31	T5	Y	3	IC	4–6	0	62.2	56	66.7	45.8	45.8	66.9
5	M	37	C7	N	11	IC	6+	0	40.9	40.9	40.9	45.8	45.8	45.8
6	M	39	L1	Y	16	IC	1–3	4	62.9	59.8	65.9	64.4	61.3	64.4
7	F	33	T9	N	3	IC	6+	2	57	57	57	63.1	45.8	45.8
8	M	42	T10	Y	25	IC	6+	0	65.9	40.9	54.8	66.2	45.8	45.8
9	M	32	T10	Y	5	IC	6+	0	–	–	–	–	–	–
10	M	18	C5	N	0	IDC	6	–	–	–	–	–	–	–
Median/Mean		35/33.3			8/8.9		6/4.5	0/1	60.6/57.3	53.9/50.5	55.9/55.7	54.4/54.4	45.8/50.1	45.8/51.6
Arm A + B														
Median/Mean		33/31.3			4/8.9		6/4.5	0/1	60.6/57.3	53.2/51.1	54.8/54.8	54.4/54.4	45.8/50.2	45.8/50.1

Arm B

Demographics and outcomes are recorded in Table 2. Participants were young and many years post SCI, all were managing their neurogenic bladder with self-IC, and had median 6 UTIs in the last 12 months. Four participants remained free of UTI in the 24 weeks of the trial. Bladder Management Difficulties and Bladder Complication T-scores had a mean reduction from baseline 57.3 and 54.4, of 6.8 and 4.3 at 12 weeks and 1.6 and 2.8 at 24 weeks, respectively. At the end of study survey, 5/6 said installations were not bothersome at all, and all were glad they participated in the study. Since instillations finished, comments were "my bladder health was generally better until I got a UTI", "I haven't had a UTI for a couple of months", and "it seems that I'm more at risk of UTI since HA + CS stopped." Two participants reported an intention to remain on HA + CS supervised by their general practitioner. Other comments were that the HA + CS packaging was difficult to open and that a three-way tap would help by allowing the HA + CS syringe to be attached to the catheter before insertion into the bladder.

Adverse events

Thirteen adverse events were recorded, 8 within 24 h of instillation. Twelve were of mild severity. The most common AE was cloudy urine +/- urinary sediment, usually noted with the IC following intravesical HA + CS, and resolving within 24 h. (see Table 3).

Discussion

The current study shows intravesical HA + CS in people with SCI is feasible. It did however reveal significant barriers to recruiting acute patients within 10 days of SCI, with only 2/33 screened individuals completing the 24-week study. This is partly a reflection of our exclusion criteria of age >70 years and the requirement for informed patient consent. Given that specialist nursing staff could administer HA + CS for the hospitalized period, an upper age limit for exclusion may not be necessary. For patients unable to give informed consent, this could be obtained from relatives.

In contrast, recruitment of people with chronic SCI was more successful; there was a larger population to draw from, bladder management was established, and they were clinically stable. They had also recognized the reduced quality of life associated with recurrent UTI,[22] in contrast to people with acute SCI who were adjusting to the various implications of an SCI diagnosis. Although we recruited individuals managed by self-IC, HA + CS could also be utilized and studied in

Table 3 Adverse events following intravesical hyaluronic acid + chondroitin sulphate (HA + CS).

Timing of AE	Description	Severity	Relationship to HA + CS	Outcome
<24 h	Nausea/chills/headache	Mild	Unlikely	Resolved
<24 h	Headache/fatigue	Mild	Unlikely	Resolved
<24 h	Bladder spasms	Mild	Suspected	Resolved
<24 h	Cloudy urine/ bladder pain	Mild	Suspected	Resolved
<24 h	Cloudy urine/sediment	Mild	Suspected	Resolved
<24 h	Cloudy urine	Mild	Suspected	Resolved
<24 h	Sediment in urine	Mild	Suspected	Resolved
<24 h	Sediment in urine	Mild	Suspected	Resolved
<7 days	UTI	Mild	Suspected	Antibiotics
<7 days	Bladder pain/cloudy urine	Mild	Unlikely	Resolved
<7 days	Bladder pain	Mild	Unlikely	Resolved
>7 days	Chest infection	Moderate	Unlikely	Antibiotics
>7 days	Infected SPC site	Mild	Unlikely	Resolved

AE = adverse event, SPC = suprapubic catheter, UTI = urinary tract infection.

people with SPC or IDC. Most participants reported that installation was easy or very easy and the adverse risk profile was predominated by short-term mild cloudy urine, which leads us to suggest HA + CS could be administered by individuals at home after initial education and supervision. This would also make HA + CS more accessible to individuals residing in remote locations-one such person was excluded from Arm B of this study. The study was not powered to examine efficacy, but four out of eight chronic SCI participants were free of UTI in the 24 weeks of the study in contrast to frequent UTIs (median 6, mean 4.5) in the 12 months before the study. These findings support two small studies of 10 and 11 people with chronic neurogenic bladder that suggested effectiveness of HA + CS at reducing UTI incidence.[17,18] Indeed, systemic review and meta-analysis demonstrated efficacy in non-injured women with recurrent UTI.[23] Quality of life scores in the chronic SCI group were also improved during the treatment period. Numbers were too small in the acute SCI group to comment on efficacy.

Larger case–control or randomized controlled trials in SCI should be undertaken to properly examine efficacy for preventing UTI. Ideally trials would be placebo-controlled because this cohort of patients are often desperate for an intervention to be effective, and this may lead to a significant placebo effect. Also the diagnosis of UTI needs to be robust according to recognized criteria as symptoms may occur due to pathologies other than UTI, and bacteriuria alone is not sufficient to diagnose UTI. While establishing the protocol appeared to be easier in a chronic SCI population, overcoming barriers to commencing HA + CS prophylaxis in acute SCI may provide long-term benefits, since lengthening the time to first UTI may reduce subsequent UTI rates [12]. Antibiotic prophylaxis was effective in reducing UTI in several studies of people with neurogenic bladder after SCI, although antibiotic resistance was demonstrated,[11,24,25] and other studies did not show efficacy.[24] Options for antimicrobial prophylaxis following SCI include fosfomycin which has a very high urinary and a broad activity against uropathogens, although it was not effective at preventing UTI after kidney transplantation.[26] Sublingual vaccines containing inactivated uropathogens have been shown to greatly reduce UTI in women with recurrent UTI,[27–29] and may warrant investigation in those with SCI.

In summary, we have demonstrated that recruitment to studying HA + CS in neurogenic bladder due to SCI is easier in chronic SCI than acute SCI. In addition, individuals can self-administer without serious adverse events, with a suggestion it may be effective. Larger trials of HA + CS in this group are warranted to evaluate efficacy.

Conflicts of interest

No potential conflict of interest was reported by the author(s).

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Author contributions

GK King: Project development, data collection, data analysis, manuscript writing; LM Goodes: project development, data collection, data analysis, manuscript writing; C Hartshorn: project development, data

collection, manuscript writing; J Thavaseelan: project development, manuscript writing; S Jonescu: data collection; A Watts: project development, data collection; M Rawlins: project development, data analysis, manuscript writing; P Woodland: project development, manuscript writing; E-L Synnott: project development, data analysis, manuscript writing; T Barrett: project development, manuscript writing; D Hayne: project development, manuscript writing; P Boan: project development, data collection, data analysis, manuscript writing; SA Dunlop: project development, data collection, data analysis, manuscript writing.

Data deposition

Data is completely supplied in this manuscript. There is no supplemental data.

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