Acute spontaneous spinal cord infarction: Utilisation of hyperbaric oxygen treatment, cerebrospinal fluid drainage and pentoxifylline

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Abstract
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Introduction: Spinal cord infarction (SCI) is a potentially devastating disorder presenting with an acute anterior spinal artery syndrome, accounting for an estimated 1% of stroke presentations. Aetiologies include aortic surgical complications, systemic hypotension, fibrocartilaginous embolism and vascular malformations. Diagnosis is clinical combined with restriction on diffusion-weighted magnetic resonance imaging (MRI). There are no treatment guidelines for non-perioperative cases although there is limited literature regarding potential therapies, including hyperbaric oxygen treatment (HBOT) and cerebrospinal fluid (CSF) drainage. We describe 13 cases of acute SCI, five receiving HBOT, and three also receiving pentoxifylline and drainage of lumbar CSF.

Methods: Data for all patients with MRI-proven SCI at Fiona Stanley Hospital from 2014–2019 were reviewed.

Results: Thirteen patients, median age 57 years (31–74), 54% female, were identified. Aetiologies: two fibrocartilaginous emboli; seven likely atherosclerotic; two thromboembolic; two cryptogenic. All presented with flaccid paraplegia except one with Brown-Sequard syndrome. Levels ranged from C4 to T11. Five patients received HBOT within a median time of 40 hours from symptom onset, with an average 15 treatments (10–20). Three of these received triple therapy (HBOT, pentoxifylline, CSF drainage) and had median Medical Research Council manual muscle testing power of 5, median modified Rankin Score (mRS) of 1 and American Spinal Injury Association (ASIA) score of D on discharge, compared with 2 power, mRS 3.5 and ASIA B in those who did not.

Conclusions: SCI can be severely disabling. Triple therapy with pentoxifylline, CSF drainage and HBOT may reduce disability and further prospective trials are required.

Introduction

Spinal cord infarction (SCI) is a rare but potentially devastating disorder accounting for an estimated 1% of all stroke presentations.[1] The typical clinical presentation is that of an anterior spinal artery syndrome with acute flaccid paraparesis or quadriparesis, loss of pain and temperature sensation below the level of the lesion and autonomic dysfunction of the bladder and bowel, developing over minutes to hours. There is a broad array of potential aetiologies, with the most common being the peri-operative complication of thoraco-abdominal aortic aneurysm repair. Other causes can be divided into: intrinsic arterial occlusion (secondary to embolism, thrombosis, atherosclerosis), systemic hypo-perfusion, and venous infarction (usually due to arteriovenous malformations). Fibrocartilaginous embolism (FCE) from herniated intervertebral discs is an increasingly recognised cause of embolic spinal cord infarction, although likely under-diagnosed.[2–4] The diagnosis is made clinically, supported by diffusion-weighted magnetic resonance imaging (DW-MRI). Conventional MRI sequences are often not sufficiently sensitive in the acute phase.[5]

Treatment guidelines are available for iatrogenic cases associated with aortic aneurysm repair, and revolve around improving spinal cord perfusion via a combination of blood pressure support and lumbar drainage of cerebrospinal fluid (CSF), but there are no similar treatment guidelines for spontaneous acute spinal cord infarction.[6–8] Animal models mimicking post-operative SCIs have shown neuro-protective effects from various medications, including pentoxifylline, corticosteroids, mannitol and iloprost, although clinical data have not proven their effectiveness.[9–11] Hyperbaric oxygen

treatment (HBOT) has also shown promise in animal models, but there is a paucity of high level evidence to support its use, despite multiple case reports of good outcomes when used in the post-operative infarction population.[10,12,13]

This case series describes 13 cases of spontaneous acute spinal cord infarction at Fiona Stanley Hospital (FSH), five of whom received HBOT, of which three also received pentoxifylline and drainage of lumbar CSF.

Methods

This retrospective audit was approved by the institutional review board of FSH, Murdoch, Western Australia: Quality Activity 33011.

We identified through the hospital database all patients who had been admitted to FSH with a diagnosis of spinal cord infarction from October 2014 to October 2019. Patients with spinal cord infarction secondary to a surgical procedure were excluded as treatment protocols already exist for this cohort. Any patients without DW-MRI evidence of spinal cord infarction were also excluded.

We retrospectively collected data on clinical presentation, treatment and clinical course from the FSH electronic medical record. All clinical details and evaluations were gathered from the notes of the treating neurologists, rehabilitation specialists and physiotherapists. This included demographics and comorbidities, predisposing risk factors including trauma, as well as assessment of neurological deficits on presentation and at discharge using Medical Research Council (MRC) manual muscle testing, the American Spinal Injury Association (ASIA) Score and the modified Rankin Score (mRS). Data regarding investigations performed, treatment received (both pharmacologic and hyperbaric), as well as weeks of rehabilitation required, were also recorded.

Results

A total of 13 patients met the study criteria (see Table 1), with a median age at presentation of 57 years (range 31–74); seven (54%) were female. All but one patient presented with bilateral flaccid lower limb weakness, urinary retention and constipation. One patient presented with a Brown-Sequard syndrome. Eight patients had complete paraplegia with MRC manual muscle testing power of zero out of five (no movement) and ASIA score A, with the remaining patients having incomplete motor deficits of ASIA score C (n = 4) or D (n = 1). Affected spinal cord levels ranged from C4 to T11, with four patients having cervical level involvement.

AETIOLOGY AND RISK FACTORS

Seven patients were thought to have SCI secondary to atherosclerosis. These patients were older with a median age of 68 years (54–74), majority male (n = 5). All had comorbid hypertension and dyslipidaemia, with four also having a previous smoking history. Two patients had type 2 diabetes mellitus and one had a previous internal capsule lacunar stroke.

FCE was the putative aetiology in two patients, with both having performed heavy lifting in the week prior to presentation: Patient 1 had onset of pain and weakness directly after a CrossFit® workout; Patient 2 experienced back pain one week prior to presentation after lifting heavy boxes then had chiropractic manipulation the day before onset of lower limb weakness.

Two patients were considered to have thromboembolic SCIs, with one patient found to have antiphospholipid syndrome on thrombophilia screening, the other patient had a persistent foramen ovale and lower limb deep vein thrombosis, causing paradoxical embolus to the spinal cord.

There were two cases of cryptogenic SCI: one case with negative investigations including transthoracic echocardiogram, 24-h cardiac Holter monitoring, vasculitis and thrombophilia screening; another case with multiple competing aetiologies including FCE from a recent knee meniscal tear or marantic endocarditis with positive anti-nuclear antibodies (20 $IU \cdot ml^{-1}$) with a homogenous pattern, but no other features suggestive of systemic lupus erythematosus including a negative anti-dsDNA and normal complement levels.

TREATMENT

All patients received standard therapy of initial antiplatelet therapy with 100 mg aspirin and best supportive medical care on the tertiary neurology ward. Four patients also initially received treatment for suspected transverse myelitis with intravenous methylprednisolone without effect. Five patients received HBOT, all commencing within 48 h of symptom onset (mean 32 h, range 10–48) and continuing daily until a plateau in improvement was reached (defined as no further clinical improvement over 48 h): median 15 treatments (range 12–20). All patients were treated initially at 284 kPa (2.8 atmospheres absolute [atm abs]) for at least two treatments then at 243 kPa (2.4 atm abs) or 203 kPa (2 atm abs). Three of these five patients received a 'triple therapy' combination of HBOT, pentoxifylline 400 mg three times per day for five days, and CSF lumbar drainage either from a lumbar spinal drain (n = 1) or recurrent lumbar punctures, draining 20–40 ml of CSF twice (n = 2). Triple therapy was initiated in tandem, as soon as possible, with the initial lumbar punctures performed prior to HBOT.

OUTCOMES

All but one patient undertook a period of inpatient rehabilitation, requiring a median time of 7.5 weeks (range 0–15) to achieve a median mRS of 2 (range 0–5). MRC muscle power grade on discharge from rehabilitation ranged

from 0 to 5 (median 4-). An ASIA score of A (complete motor and sensory deficit) was given in five patients, while six patients had a score of D. The patient who did not receive rehabilitation chose to return to their country of origin after acute therapy was completed and was lost to follow-up.

Patients who recovered to a state of independence (n = 7), defined as an mRS ≤ 2 were more likely to be of younger age (median 46 y, range 31–69), female (five, 71%) and have an aetiology other than atherosclerosis (two FCE, one thromboembolism, two cryptogenic, two atherosclerosis). This group of patients required a median rehabilitation time of three weeks (range 0–14) to achieve a median mRS of 2 (range 0–2) and ASIA D score.

Recipients of HBOT required a median of 3.5 (0–14) weeks rehabilitation to achieve a median mRS of 2 (0–4) and ASIA scores of A (n = 1), D (n = 3) and E (n = 1) on discharge. The patient with the ASIA A score had a SCI secondary to atherosclerosis and was comparatively older at 56 y, compared with a median age of 35 y (31–46) in the remaining four patients.

The patients who received triple therapy appeared to have better outcomes on discharge with a median mRS score of 1 (0–2) and median MRC muscle power of 5- (4+ to 5). These patients were younger (mean age 35, 35–46 y) and had ASIA scores of A (n = 1) and C (n = 2) on presentation (see Table 1 and Figure 1).

Discussion

We present a retrospective case series of spontaneous acute SCI, detailing our experience in treating this relatively uncommon and potentially devastating disorder. The majority of previous cohorts and case studies have included SCI resulting from surgical complications. We excluded these patients from our study to focus on medical presentations, where there are currently no accepted treatment protocols. In this cohort of patients, the initial diagnosis of SCI is not always clear from that of transverse myelitis or other causes of acute flaccid paraparesis, in some part explaining the delay to treatment initiation and why four of the 13 patients also received initial therapy with methylprednisolone.

The cohort was comprised mainly of SCIs associated with vascular risk factors, thought to be secondary to atherosclerosis, consistent with previous reports.[14,15] Interestingly, two out of the 13 cases were of FCE, in keeping with recent evidence that this is an increasingly recognised cause of SCI.[2] In the age of CrossFit® and the rising popularity of heavy weightlifting exercises, it is important for clinicians to be cognisant of the potential for FCE to cause spinal cord ischaemia, as in our patient who performed a CrossFit® workout immediately prior to developing a C6 complete paraplegia.

Post-operative SCI as a complication of aortic surgery has a standardised treatment protocol involving vasopressor support of blood pressure and CSF lumbar drainage to maintain spinal cord perfusion.[6,16] In the present cohort we describe three patients who had excellent outcomes following a combination of recurrent CSF drainage (with a lumbar drain or recurrent high-volume lumbar punctures), pentoxifylline and HBOT; a combination we have named 'triple therapy' for the purposes of this article. This combination is based on case reports showing improved outcomes with HBOT in post-operative SCI, as well as animal models of spinal cord ischaemia showing potential benefit of pentoxifylline, combined with the accepted benefit of CSF drainage in acute post-operative spinal cord infarction. These patients were of younger age and with SCIs of varying aetiologies: FCE, thromboembolism and cryptogenic, and their excellent outcomes returning to independent ambulation and ASIA score D-E emphasises the need for further investigation of this treatment combination in prospective studies.

HBOT is another prospective treatment, used in five of our patients, after multiple case reports have suggested benefit in the mostly post-operative SCI population where treatment can be initiated as soon as symptoms are recognised.[10,12,13] Selecting patients with medical or spontaneous SCI for HBOT provides further challenges as the diagnosis must be suspected on presentation and then access to HBOT must be established. In Western Australia, our centre acts as the sole quaternary referral centre for HBOT, with hyperbaric physicians providing a 24/7 service. Despite this, in these five patients, there was still a median time delay between symptom onset and HBOT initiation of 31 hours (range 10–48), related to delayed diagnosis and referral. Patients were continued on daily HBOT until a plateau of clinical neurological recovery was reached. This treatment protocol is based on the treatment protocols for spinal decompression illness and other acute ischaemic conditions treated with

Figure 1

Patient Subgroup Outcomes. Post-treatment median Medical Research Council (MRC) manual muscle testing power, modified Rankin score, and ASIA scores, across the three subgroups of patients that received HBOT plus standard care, Triple Therapy (of HBOT, CSF drainage and pentoxifylline), or standard care alone. The corresponding numerical ASIA scores are as follows: 1 = A, 2 = B, 3 = C, 4 = D, 5 = E

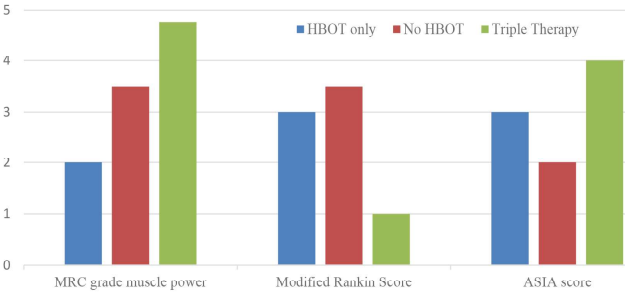

Table 1

Cohort data. HBOT (hyperbaric oxygen treatment) is listed as number of treatments at each pressure, as well as the total time of pressurised treatment in minutes. Patient one completed one 90 min and four 60 min treatments at 284 kPa and twelve 60 min treatments at 243 kPa, for a total duration at pressure of 3,516 minutes. Patient two: two 60 min treatments at 284 kPa and eight 90 min treatments at 243 kPA. Patient three: five 60 min treatments at 284 kPa and fifteen 120 min treatments at 202 kPa. Patient four: One 120 min and twelve 60 min treatments at 284 kPa and three 90 min treatments at 243 kPa. Patient five: three 90 min and five 60 min treatments at 284 kPa and four 90 min treatments at 243 kPa. ANA = anti-nuclear antibodies, ASIA = American Spinal Injury Association score (A = complete motor and sensory deficit, E = normal), bd = twice daily, C = cervical, DVT = deep vein thrombosis, dsDNA = double-stranded deoxyribonucleic acid antibodies, ENA = extractable nuclear antibodies, FCE = fibrocartilaginous embolism. MRC = Medical Research Council manual muscle testing power (out of 5), mRS = modified Rankin Score (out of 6, 0 = no symptoms, 2 = independent, 4 = unable to ambulate independently, 5 = bedridden), T = thoracic

Patient	Age/ Sex	Risk factors	Aetiology of infarct	Spinal level	ASIA on admission	MRC power on admission	Significant results	Treatment	HBOT treatments (total duration)	HBOT: Time delay (hours)	MRC power post-rehabilitation	Duration of rehab (weeks)	mRS on discharge	ASIA on discharge
1	35F	Nil	Thrombo-embolic	C4	A	0	Anti-cardiolipin antibody positive, low C3 and C4	Methyl-prednisolone, aspirin, pentoxifylline, inotropic support to mean arterial pressure > 70, 2 x 40 ml lumbar punctures, anticoagulation from day 14	284 kPa x 5 + 243 kPa x12 (3516 min)	10	4+	6	2	D
2	46F	Knee meniscal tear	Cryptogenic	T3	C	3	ANA strong positive, ENA and dsDNA negative. Marantic endocarditis seen on echocardiogram	Aspirin, pentoxifylline, lumbar drain	284 kPa x 2 + 243 kPa x 8 (2064 min)	40	5-	8	1	D
3	35M	Heavy lifting one week previous, smoker	FCE	T8	C	2		Methyl-prednisolone, aspirin, pentoxifylline, 2 x 20ml lumbar punctures	284 kPa x 5 + 202 kPa x 15 (5280 min)	48	5	0	0	E
4	31F	CrossFit® workout	FCE	C6	A	0	Heterozygous for prothrombin G20210A gene mutation	Aspirin	284 kPa x 13 + 243 kPa x 3 66 (3000 min)	48	1+	14	2	D

Table 1 continued.

5	57M	Hypertension, dyslipidaemia, obesity, obstructive sleep apnoea	Athero-embolic	T1	A	0		Methyl-prednisolone, aspirin	284 kPa x 8 + 243 kPa x 4 (1620 min)	14	2+	12	4	A
6	54M	Previous stroke, dyslipidaemia, insulin resistance	Athero-embolic	T6	C	2.5	Persistent foramen ovale on echocardiogram	Aspirin	0	n/a	3+	15	3	C
7	56M	Dyslipidaemia	Thrombo-embolic	T4	A	0	Persistent foramen ovale on echocardiogram, lower limb DVT	Aspirin, enoxaparin 70 mg bd	0	n/a	0	12	5	A
8	69M	Hypertension, dyslipidaemia, ex-smoker	Athero-embolic	T2	C	3	Heterozygous factor V Leiden, positive cardiolipin IgM, infero-basal hypokinesis on echocardiogram	Aspirin	0	n/a	4+	2.5	1	D
9	76M	Hypertension, dyslipidaemia, T2DM, ex-smoker	Thrombo-embolic	T6	A	0	Atrial fibrillation on cardiac monitoring	Aspirin	0	n/a	0	7	5	A
10	68F	Hypertension, hormone replacement therapy, dyslipidaemia, ex-smoker	Athero-embolic	C5	A	0		Aspirin	0	n/a	4	3	2	D
11	69F	Hypertension, dyslipidaemia, family history of ischaemic heart disease	Athero-embolic	T9	A	0		Aspirin	0	n/a	n/a	n/a	4	A
12	64M	Obesity, hypertension	Athero-embolic	C5	A	0		Aspirin	0	n/a	2	12	4	A
13	61F	Nil	Cryptogenic	T7	D	4		Methyl-prednisolone, aspirin	0	n/a	4	2	2	D

HBOT. Unlike typical post-operative SCI cases, there was a potentially significant delay in treatment initiation in these patients. HBOT is purported to reduce ischaemia by inducing arterial vasoconstriction, thereby reducing tissue oedema whilst maintaining tissue oxygenation and by anti-inflammatory mechanisms reducing ischaemia-reperfusion injury.[17] The potential benefit is seen in preventing secondary neuronal injury and therefore, the earlier the initiation of HBOT, the greater the potential benefit.

Similar antioxidant properties reducing secondary neuronal injury are theorised to be associated with pentoxifylline therapy: improving microcirculation by decreasing blood viscosity and increasing erythrocyte flexibility, while also reducing neutrophil activation and adhesion to reduce ischaemia-reperfusion injury.[11,18] There are no clinical data confirming its effectiveness in patients with acute spontaneous SCI.

As a case series, subgroup analysis is not possible and it is important not to over-interpret the results, but there appears to be a trend towards better outcomes in patients who received 'triple therapy'. We propose that further prospective studies explore this new treatment protocol, particularly that of CSF drainage and HBOT, both of which have case report level data to support use in SCI. It is important to acknowledge that this may not be feasible due to limited access to HBOT at other centres; and that, as per the guidelines written by The International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP) panel in 2007, such studies would require a very large sample size to accurately assess the significance of triple therapy in improving functional outcomes in spontaneous SCI.[19]

Conclusions

Spontaneous SCI can be severely disabling and recovery is often incomplete. Aetiologies across this group are heterogeneous, and fibro-cartilaginous embolism is likely an under-recognised cause. 'Triple therapy' of CSF drainage, HBOT and pentoxifylline may be a promising new treatment protocol for spontaneous SCI and should be prospectively investigated.

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