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Strict Control of Blood Glucose With an Intravenous Insulin Infusion Decreases the Risk of Post-operative Lower Extremity Weakness After Complex Endovascular Aortic Aneurysm Repair☆

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WHAT THIS PAPER ADDS

This observational cohort study shows that controlling blood glucose levels with an intravenous insulin infusion after branched endovascular aneurysm repair is associated with a decreased risk of post-operative lower extremity weakness. Tight control of blood glucose should be considered in patients undergoing extensive endovascular aortic procedures to minimise the risk of post-operative lower extremity weakness.

Objective/background: It has previously been shown that post-operative lower extremity weakness (LEW) is associated with elevated blood and cerebrospinal fluid (CSF) glucose levels after branched endovascular aneurysms repair (BEVAR) of extensive aortic aneurysms. The purpose of this study was to determine whether a post-operative insulin infusion protocol (IIP) to achieve tight blood glucose control decreases the rate of LEW.

Methods: From October 2013, blood and CSF samples were collected pre-operatively, immediately post-operatively, and on post-operative day one in asymptomatic patients undergoing BEVAR. In July 2016, an IIP was initiated to maintain post-operative blood glucose levels $<$120 mg/dL for 48 h. Data on demographics, operative repair, complications, and outcomes were collected prospectively.

Results: Between October 2013 and April 2018, 43 patients underwent BEVAR. Twenty-two (group A) underwent BEVAR before initiation of the IIP. Of these, seven (32%) developed LEW within 48 h of repair. This was temporary in five (23%) and permanent in two (9%) patients. Post-operative blood glucose levels were significantly higher in patients with LEW compared with those without LEW (140 $\pm$ 27 mg/dL vs. 117 $\pm$ 16 mg/dL; $p = .02$). Post-operative CSF glucose levels were significantly higher in patients with LEW compared with those without LEW (102 $\pm$ 15 mg/dL vs. 77 $\pm$ 15 mg/dL; $p = .001$). The subsequent 21 patients (group B) underwent BEVAR after initiation of the IIP. No patient in group B developed LEW while on the IIP, but one (5%) developed paraplegia on post-operative day four. The rate of early LEW ($<$48 h post-operatively) was significantly lower after initiation of the IIP (32% in group A vs. 0% in group B; $p = .009$). There was no difference in demographics, comorbidities, or operative time between the groups.

Conclusion: An IIP to control blood glucose after BEVAR is associated with a decreased rate of post-operative LEW. Tight control of blood glucose should be considered after any extensive aortic reconstruction to minimise the risk of post-operative LEW.

Keywords: Branched endovascular aortic aneurysm repair, Glucose control, Intravenous insulin infusion, Thoraco-abdominal aortic aneurysm repair
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INTRODUCTION

Paraplegia remains a devastating complication after complex endovascular procedures to repair thoraco-abdominal aortic aneurysms (TAAA). Known risk factors for spinal cord ischaemia (SCI) after endovascular TAAA repair include increased length of aortic coverage, hypotension, coverage of important collateral vessels, and a "shaggy" aorta prone to embolisation.[1–6] Even with multimodal strategies to address these risk factors (staging extensive procedures whenever possible, allowing permissive hypertension in the peri-operative period, revascularisation of the left subclavian and hypogastric arteries, minimising manipulation within a diseased aorta, and routine drainage of cerebrospinal fluid [CSF]),[7–9] paraplegia still occurs in approximately 5–10% of these patients.[5–7] The rates of transient lower limb weakness are even higher.[10–12]

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Possible metabolic risk factors for SCI have not been studied extensively. Multiple studies have examined the association between hyperglycaemia and clinical outcomes after acute ischaemic stroke and severe head injury,[13–17] but the study of hyperglycaemia as a risk factor for SCI has been limited mostly to animal studies. In a study of acute SCI, hyperglycaemic mice developed more severe motor deficits compared with normoglycaemic mice.[18] Interestingly, the detrimental effects of hyperglycaemia were prevented by normalisation of the blood glucose with insulin during the acute phase of SCI. In a spinal tumour model, hyperglycaemic rats required a lower epidural tumour volume and had a decreased time to paralysis vs. normoglycaemic rats.[19]

The possible mechanisms by which hyperglycaemia exerts its deleterious effects in the brain and spinal cord include increased anaerobic metabolism with lactic acid production, free radical formation with oxidative injury, inflammation, or disruption of the blood brain barrier (BBB).[20–23] It is not clear whether elevated glucose levels are directly toxic to neuronal cells or if hyperglycaemia is a biomarker of injury severity. If the former is true, then normalising blood glucose levels with an insulin infusion may protect neurons from injury. Or, it is possible that insulin could be attenuating neuronal damage independent of glucose levels. Insulin receptors are abundant throughout the central nervous system (CNS) and insulin is known to have many pleiotropic effects. Insulin is a key neuromodulator in the brain,[24,25] has anti-inflammatory properties,[26–28] may decrease disruption of the BBB,[29] and plays a role in inhibiting neuronal apoptosis.[30–34]

It has been shown previously that elevated blood and CSF glucose levels were significantly associated with post-operative lower extremity weakness (LEW) in patients undergoing branched endovascular aneurysm repair (BEVAR) of TAAA and pararenal aortic aneurysms (PRAA).[10] In July 2016, an insulin infusion protocol (IIP) was instituted to maintain post-operative blood glucose levels $\leq$ 120 mg/dL for 48 h. The purpose of this current study was to determine whether the use of an IIP to achieve tight blood glucose control decreases the rate of LEW after BEVAR.

MATERIALS AND METHODS

In July 2005, a prospective clinical trial of endovascular repair of PRAA and TAAA using a multibranched aortic stent graft (Cook Australia, Brisbane, Australia) was started. This study was performed under a physician sponsored investigational device exemption approved by the Food and Drug Administration and the Committee on Human Research at the University of California, San Francisco (UCSF), United States of America. Details of the study design, inclusion and exclusion criteria, surgical technique, data collection, and clinical outcomes have been published previously.[35,36] All patients in this study underwent endovascular aneurysm repair using branched stent grafts. As a result, the proximal seal zone was in the supracoeliac aorta, even in patients with type IV TAAA or PRAA.

All patients were admitted to the hospital one day prior to BEVAR and hydrated with intravenous fluids. Antihypertensive medications were routinely withheld peri-operatively. All patients underwent pre-operative placement of a lumbar catheter to drain CSF. Intra-operatively, CSF was drained at a rate of 10 mL/h. An additional 10 mL CSF was drained after insertion of the final branch of the BEVAR. CSF drainage was continued at 10 mL/h for the first 24 h after surgery; subsequent management of the CSF drain was dependent on the neurological status. Antegrade flow was maintained to the subclavian and internal iliac arteries through bypass graft procedures prior to definitive BEVAR. During BEVAR, the large sheaths placed through the femoral arteries to deliver the aortic components were removed and the femoral artery access sites repaired in order to restore perfusion to the pelvis and lower extremities, prior to insertion of the branches from the arm. Patients were transfused with packed red blood cells to achieve a haemoglobin target of 10 g/dL in the first 48 h after surgery.

A neurologicalal examination was performed immediately after conclusion of BEVAR on awakening from general anaesthesia. All patients were admitted to the intensive care unit (ICU) after BEVAR and a neurologicalal assessment was performed by the ICU nurse every hour. A neurological examination was also performed on a twice daily basis by the surgical team and any time there was noted to be a change in examination findings.

Patients who developed LEW were treated with immediate, additional CSF drainage until symptoms improved or the patient developed a headache. A maximum of 50 mL CSF was removed over 60 min. The patient was concurrently treated with administration of blood products and/or intravenous fluids to augment the systemic blood pressure. Vasoactive medications were only initiated if the patient continued to be symptomatic after these manoeuvres.

LEW was a predefined adverse event. The onset of LEW was categorised as either intra-operative or post-operative, and transient or permanent. If the patient awoke from anaesthesia with a neurological deficit, this was defined as intra-operative. If the patient had a normal neurological examination upon awakening from anaesthesia but subsequently developed a neurological deficit, this was defined as post-operative. A neurological deficit that resolved within 30 days from surgery was defined as transient, and a deficit lasting beyond 30 days was defined as persistent. Paraplegia was defined as the inability to stand without assistance.

In October 2013, collection of blood and CSF samples was started pre-operatively, immediately post-operatively, and on post-operative day (POD) one in fasting patients who underwent elective BEVAR for PRAA or TAAA. Blood samples were obtained from an indwelling arterial catheter and either immediately analysed or centrifuged at 3000 rpm for 15 min and stored in aliquots at $-80\ ^{\circ}C$ until the time of analysis. CSF samples were collected from an indwelling lumbar catheter and either immediately analysed or centrifuged at 2000 rpm for 10 min and stored in aliquots at $-80\ ^{\circ}C$ until the time of analysis. All samples were analysed by the UCSF Clinical Laboratories using the

Table 1. Demographic characteristics of patient cohort undergoing branched endovascular aneurysm repair prior to (group A) and after initiation (group B) of insulin infusion protocol.

	Group A (n = 22)	Group B (n = 21)	p
Mean ± SD age (y)	73.1 ± 8.1	72.3 ± 5.6	.71
Male	17 (77)	12 (57)	.20
Diabetes mellitus	4 (18)	4 (19)	1.0
Hypertension	22 (100)	20 (95)	.49
Hyperlipidaemia	18 (82)	17 (81)	1.0
Stroke/transient ischaemic attack	6 (27)	3 (14)	.46
Chronic kidney disease (glomerular filtration rate < 60 mL/min)	7 (32)	5 (24)	.74
Lung disease	15 (68)	16 (76)	.74
Current/past smoking	21 (95)	20 (95)	1.0
Peripheral artery disease	3 (14)	3 (14)	1.0
Cardiac disease	13 (59)	11 (52)	.88
Staged repair	11 (50)	11 (52)	1.0
Modified Crawford Classification			.94
I	2 (9)	1 (5)	
II	5 (23)	3 (14)	
III	3 (14)	3 (14)	
IV or pararenal	11 (50)	12 (57)	
V	1 (4)	2 (10)	
Mean ± SD maximum aneurysm diameter (mm)	64 ± 8	64 ± 5	.75

Note. Data are n (%) unless otherwise indicated. SD = standard deviation.

Synchron System (Beckman Coulter, Brea, CA, USA). Glucose levels were analysed using an oxygen rate method with a Beckman Coulter oxygen electrode, with an analytic range of 10—600 mg/dL, within run coefficient of variation (CV) of 2.0%, and total CV of 3.0%.

In July 2016, an IIP was initiated in order to maintain post-operative blood glucose levels <120 mg/dL for 48 h. Glucose levels were checked immediately on arrival in the ICU and every hour. A continuous intravenous infusion of regular insulin was started in the ICU if any post-operative blood glucose was found to be ≥ 120 mg/dL. The starting infusion rate was 0.5 unit/hour if glucose was 120—150 mg/dL; 1.0 unit/hour for a glucose level of 151—200 mg/dL; 1.5 units/hour for a glucose level of 201—300 mg/dL; 2.0 units/hour for a glucose level of >300 mg/dL. The insulin infusion rate was further titrated based on subsequent glucose measurements. The IIP was continued in the ICU for the first 48 h post-operatively.

Statistical analysis was performed with STATA/SE version 10.1 (StataCorp, College Station, TX, USA). Continuous variables were compared using a Student t test and categorical variables were compared using Fisher's exact test. A p value < .05 was considered statistically significant.

RESULTS

Between October 2013 and April 2018, 45 patients underwent successful elective BEVAR. Two patients had pre-existing paraplegia from prior open aortic surgery and were excluded from this study, leaving 43 patients for the current analysis. The mean age of the study group was 72.7 ± 7.0 years and 29/43 (67%) were men. Eight (19%) had diabetes mellitus; four were on oral medications, four were diet controlled, and none was taking insulin pre-operatively. Forty-two (98%) had a history of hypertension, nine (21%) had a history of previous transient ischaemic attack or stroke, and 41 (95%) were current/former smokers. The mean aneurysm diameter was 64 ± 7 mm and 23 (54%) had a type IV TAAA or PRAA. Twenty-two patients (group A) underwent BEVAR *before* initiation of the IIP and the subsequent 21 patients (group B) underwent BEVAR *after* initiation of the IIP. There was no difference in demographic characteristics, medical comorbidities, aneurysm diameter, or aneurysm extent between the two groups (Table 1).

Of the 22 patients who underwent BEVAR before initiation of the IIP (group A), seven (32%) developed LEW within 48 h of repair. This was temporary in five (23%) patients and permanent in two (9%) patients (Table 2). Of the 21 patients (group B) who underwent BEVAR after initiation of the IIP, no patient developed LEW while on the IIP. One (5%) developed paraplegia on POD 4, two days after the insulin infusion had been stopped (Table 2). The rate of early LEW (<48 h post-operatively) was significantly lower after initiation of the IIP (32% in group A vs. 0% in group B; p = .009). Of note, all 21 patients in group B received intravenous insulin at some time during the first 48 h after surgery, even though none of these patients was on insulin pre-operatively. There were no differences in operative characteristics (operation duration, fluoroscopy time, or contrast volume) between groups A and B (Table 3). Although patients in group A underwent BEVAR earlier in the study period than patients in group B, there were no changes to patient selection, operative technique, or peri-operative management during the time period of this study.

In group A, mean ± SD blood glucose levels on POD one were significantly higher in patients with LEW compared

Table 2. Comparison of onset and nature of lower extremity weakness in patients undergoing branched endovascular aneurysm repair.

Group A patients	Onset	Laterality	Description
1	POD 2	Right	Transient with resolution on discharge
2	POD 1	Bilateral	Transient with resolution at follow up
3	POD 1	Left	Transient with resolution on discharge
4	4 h post-operatively	Bilateral	Permanent paraplegia
5	POD 1	Left	Transient with resolution at follow up
6	POD 2	Left	Transient with resolution at follow up
7	POD 2	Bilateral	Permanent paraplegia
Group B patient	**Onset**	**Laterality**	**Description**
1	POD 4	Bilateral	Permanent paraplegia

Note. POD = post-operative day.

Table 3. Comparison of operative details in patients undergoing branched endovascular aneurysm repair prior to (group A) and after initiation (group B) of insulin infusion protocol.

	All (n = 43)	Group A (n = 22)	Group B (n = 21)	p
Contrast volume (mL)	124 ± 50	121 ± 46	128 ± 55	.68
Operation duration (min)	372 ± 100	378 ± 83	365 ± 117	.67
Fluoroscopy time (min)	119 ± 37	126 ± 34	112 ± 40	.25

Note. Data are mean ± standard deviation (SD).

with those without LEW (140 ± 27 mg/dL vs. 117 ± 16 mg/dL; p = .02). CSF glucose levels were significantly higher in patients with LEW compared with those without LEW in the immediate post-operative period, as well as on POD one (102 ± 15 mg/dL vs. 77 ± 15 mg/dL; p = .001). Patients in group B had similar post-operative blood and CSF glucose levels as those patients in group A without post-operative LEW (Table 4).

DISCUSSION

Despite significant advances in the anaesthetic, surgical, and peri-operative management of patients undergoing complex endovascular aortic procedures, the incidence of post-operative paraplegia remains high. Strategies to decrease the incidence of SCI have focused on techniques and procedures to enhance spinal cord perfusion. The role of possible metabolic factors has not been addressed. Although hyperglycaemia has been evaluated extensively in the setting of acute ischaemic stroke, few studies have examined hyperglycaemia in acute SCI.

After initiation of the IIP in the present study, all patients required insulin at some time during the first 48 post-operative hours to maintain blood glucose levels <120 mg/dL, even though none of these patients was an insulin dependent diabetic at baseline. Hyperglycaemia occurs frequently after major surgery, and this physiological stress is associated with glucose intolerance and insulin resistance.[37–39] There is significant controversy surrounding how aggressively this post-operative hyperglycaemia should be treated, with some studies demonstrating a benefit of tight glucose control and others showing no difference in

Table 4. Blood and cerebrospinal fluid glucose values in patients with branched endovascular aneurysm repair.

	Group A lower extremity weakness (LEW) (n = 7)	Group A no LEW (n = 15)	p	Group B (n = 21)
Blood glucose (mg/dL)				
Pre-operative	117 ± 20	108 ± 24	.44	112 ± 28
Immediately post-operative	162 ± 53	142 ± 31	.27	134 ± 37
Post-operative day 1	140 ± 27	117 ± 16	.02	114 ± 22
Cerebrospinal fluid glucose (mg/dL)				
Pre-operative	67 ± 13	58 ± 13	.14	60 ± 14
Immediately post-operative	80 ± 15	66 ± 14	.03	69 ± 18
Post-operative day 1	102 ± 15	77 ± 15	.001	72 ± 19

Note. Data are mean ± standard deviation (SD).

clinical outcomes.[39,40] In addition, the optimal level of post-operative glucose levels, the length of treatment time, and the best route of insulin administration (subcutaneous vs. intravenous) have yet to be determined.

A substantial decrease in the rate of early post-operative LEW was found after an IIP was instituted in the first 48 h after BEVAR. This protective effect of insulin supplementation could be directly related to the avoidance of the adverse effects of hyperglycaemia on ischaemic neuronal tissue. In the context of SCI, elevated glucose levels may be directly toxic to ischaemic neuronal tissue, causing inflammation, mitochondrial dysfunction, and the generation of free radicals.[21,22,41,42] Hyperglycaemia may also play a role in SCI by disrupting the BBB.[43] Alternatively, the decrease in post-operative LEW may be secondary to one of the many pleiotropic effects of insulin. Insulin is derived from pancreatic β cells, transported through the BBB, and insulin receptors are found widely throughout the CNS.[44,45]

Insulin is a key neuromodulator in the brain and plays a central role in neuronal growth, differentiation, survival, and signalling.[30,46] For example, insulin plays a role in decreasing glutamate levels, which resulted in decreased infarct size and improved neuroscoring in a rat model of ischaemia.[24] Insulin also increases γ-aminobutyric acid levels, which may help to mitigate against neuronal death during brain ischaemia.[47] Insulin also has anti-inflammatory effects, which may decrease disruption of the BBB, preventing leakage of plasma proteins and inflammatory cells during ischaemia.[29] Insulin has also been shown to increase the release of endothelial nitric oxide and expression of nitric oxide synthase in endothelial cells,[48] and this vasodilatory effect could enhance the collateral vessel network and improve perfusion to ischaemic areas.

Few human studies have examined the complex interplay between glucose, insulin, post-operative stress, and SCI. In a cohort of 40 patients undergoing open TAAA repair, patients with post-operative paraplegia or paraparesis had higher CSF glucose levels after 60 min of aortic clamping than those without post-operative neurological deficits.[49] In a retrospective study of 32 patients with spinal cord stroke, higher blood glucose level on admission (regardless of diabetes mellitus) was associated with more severe spinal cord stroke.[50] Although these studies demonstrate an association between hyperglycaemia and SCI, it is not clear whether hyperglycaemia is the cause of the worsened neurological deficit, or represents the downstream effect of the injury. However, given the devastating consequences of SCI, it is felt that the potential benefit of insulin administration in these high risk patients would outweigh the negative effects (hypoglycaemia).

CONCLUSIONS

Patients with elevated blood and CSF glucose levels are at higher risk of LEW after BEVAR, and control of blood glucose levels $<$120 mg/dL with an IIP in the first 48 h after surgery is associated with a decreased rate of LEW. Tight glucose control should be considered in all patients undergoing extensive endovascular aortic procedures. The authors speculate that the post-operative hyperglycaemia after BEVAR may be due to a state of acute insulin resistance, and are currently conducting studies to better understand the mechanisms underlying this response.

CONFLICT OF INTEREST

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