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Original Article

Compartment syndrome in patients with haemophilia

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ABSTRACT

Background: Acute compartment syndrome (ACS) is an uncommon but potentially devastating condition.

Methods and results: There are scattered case reports and case series in the literature of ACS in persons with haemophilia (PWH), and even fewer in PWH and inhibitors. The management of compartment syndrome in these scenarios is controversial and often anecdotal. In addition haematological outcomes are frequently quoted but functional outcomes are generally overlooked.

This article aims to provide an overview of ACS and its contemporary management. We also review the literature and outcomes of patients with haemophilia who develop ACS in an effort to assess the best treatment modality.

Conclusion: In the majority of cases ACS settles with normalisation of the clotting cascade. Specialist haematological input is mandatory before surgical intervention should be considered, especially in PWH and inhibitors.

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1. Introduction

Richard von Volkmann first described compartment syndrome in 1881.¹ He suggested that paralysis and contracture came on simultaneously as result of an interruption to the blood supply of the affected muscles. The first surgeon to reproduce ischaemic contracture in animals was Paul Jepson in 1924² whilst working at the Mayo Foundation. He also demonstrated that prompt surgical decompression could prevent these contractures.

Acute compartment syndrome (ACS) is defined as a critical pressure increase within a confined compartmental space causing a decline in the perfusion pressure to that

compartment's tissues.^{3–6} It can occur with any elevation in interstitial pressure in a closed osseo-fascial compartment. This causes microvascular compromise and a reduction in the perfusion gradient to below a critical value, leading to ischaemia of the tissue within that compartment. ACS is now considered a surgical emergency warranting prompt evaluation and treatment.

Any internal or external event that increases intra-compartmental pressure can potentially cause a compartment syndrome. The incidence is thought to be 3.1 per 1,00,000 population, with males ten times more commonly affected than females. By far the commonest cause is trauma, and in particular tibial shaft fractures (which are more common in men). Bleeding disorders, and in particular

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haemophilia, are recognised, albeit rarer causes, which put these patients uniquely at risk of ACS often with only trivial trauma. Indeed eighty five percent of bleeding in patients with haemophilia occurs within musculoskeletal tissue. In addition a recent systematic review showed that 21% of patients with acute compartment syndrome of the thigh had coagulation defects.⁷

1.1. Overview of compartment syndrome

ACS is characterised by a critical pressure increase within a confined compartmental space causing a decline in the perfusion pressure to the compartment tissue.^{3–6} It can occur with any elevation in interstitial pressure in a closed osseofascial compartment. This causes microvascular compromise and a reduction in the perfusion gradient to below a critical value, leading to ischaemia of the tissue within that compartment. Fig. 1 below displays the cycle of events and the development of acute compartment syndrome.

Approximately 40% of all ACSs occur after fractures of the tibial shaft⁸ with an incidence in the range of 1%–10%.⁹ The next commonest location is in the forearm, but almost any compartment can be affected: arm,¹⁰ thigh,¹¹ foot,¹² buttock,¹³ hand,¹⁴ and abdomen.¹⁵ Any internal or external event that increases intra-compartmental pressure can cause a compartment syndrome. Table 1 below shows some of the more common causes.

Rorabeck reported almost complete recovery of limb function if fasciotomy was performed within six hours.¹⁶ When fasciotomy was performed within twelve hours normal limb function was regained in only 68% of patients; after twelve hours only 8% regained normal function.¹⁷

With late diagnosis irreversible tissue ischaemia develops causing potentially disastrous neurological deficits, muscle necrosis, ischaemic contracture, infection, chronic pain, delayed fracture union,¹⁸ rhabdomyolysis,¹⁷ amputation and even death.

Fig. 1 – Pathophysiology of compartment syndrome.
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Table 1 – Common causes of ACS.

Fracture	Burns
Crush injury	Infection
Injection injury	Bleeding disorders
Penetrating trauma	Arterial injury
Constrictive dressings	Reperfusion
Casts	Extravasation of drugs

ACS is a clinical diagnosis; the most important determinant of outcome is early recognition and expeditious surgical intervention. Where doubt remains the intra-compartmental pressures can be measured. Marginal pressure readings should be repeated with further compartment pressure readings and repeat physical exam. A compartment pressure of 30 mmHg less than the diastolic blood pressure is often quoted beyond this capillary pressure is insufficient to maintain muscle blood flow and the fascia has reached its maximum limitation of stretch.¹⁹

The treatment of ACS is immediate removal of all circumferential dressings down to the skin, usually followed by open fasciotomy. The limb should be kept at the level of the heart and not be elevated in the interim (or if the diagnosis is in doubt), as this decreases arterial flow and narrows the arterial-venous pressure gradient.²⁰

2. Compartment syndrome in haemophilia

Compartment syndrome is well described in persons with haemophilia (PWH) and remains a significant challenge for the haematologist and the orthopaedic surgeon. The lack of a clear aetiology or conspicuous traumatic event can contribute to the diagnostic difficulty, whilst the possibility of catastrophic bleeding makes fasciotomy potentially disastrous.

Haemorrhages located within the calf and anterior forearm represent the highest risk for the development of compartment syndrome.²¹ In patients without bleeding disorders the treatment of choice is fasciotomy, even when in doubt to prevent the establishment of motor and sensory loss, contracture and severe extremity impairment. The role of fasciotomy in haemophilia has been downplayed and care largely focuses on haemostatic manoeuvres.²²

The first step in the management of a suspected compartment syndrome should be sufficient substitution of clotting factors, which may help lower the compartment pressure.²³ Bleeding will typically tamponade before the patient experiences a substantial drop in haemoglobin. However, raised compartment pressures can cause significant morbidity in the extremities. Given the short window between symptomatic onset and tissue necrosis, early intervention is crucial and may prove to be not only limb-saving but also life-saving.

If manoeuvres to normalise the clotting derangement fail, fasciotomy is often performed to prevent muscle necrosis, joint contracture and long-term sequelae.

There are no specific pre-operative guidelines for factor replacement levels during fasciotomy, but the authors recommend 100% of normal. Infection is a significant complication usually related to persistent bleeding.

Haematological outcomes including blood loss, transfusion requirement, and clotting correction are usually reported in the literature in PWH and surgical intervention, but little is published regarding the functional or orthopaedic outcomes. Indeed clinicians often under report poor outcomes, and much of the known data and treatment policies in large haemophilia units is anecdotal.

There are scattered case reports and case series in the published literature of ACS in PWH, and even less in PWH who have inhibitors. The largest series published was by Lancourt et al.²⁴ The authors found 34 cases of bleeding into the hand and forearm in 200 PWH from 1969 to 1976. In six cases bleeding into the anterior muscles of the forearm was complicated by contracture, neuropathy, or both. Early diagnosis, replacement of the missing clotting factor, and immobilization were deemed essential. Fasciotomy was not performed in any of them.

Dumontier et al.²⁵ described 12 cases of ACS in the upper limb. They again confirmed the importance of clotting factor replacement as first line therapy. Two of the twelve patients required fasciotomy. Two patients had sequelae and incomplete recovery, and both of these were associated with late diagnosis and treatment.

Rodriguez-Merchan²⁶ reported on three patients who developed ACS. None of them required fasciotomy. In two the condition reversed with factor replacement and in the third the patient's condition was irreversible with an ulnar claw on presentation. The ACS had likely started 4 days prior to seeking medical attention. In the two treated successfully with replacement clotting factors one had a forearm contusion, the other a distal radius fracture as the initiating insult.

2.1. Compartment syndrome in persons with haemophilia and inhibitors

The development of inhibitors against replacement clotting factor is a rare but serious complication of haemophilia.²⁷ Inhibitors may develop in around 30% of patients with severe or moderately-severe haemophilia A and in 1–6% of patients with haemophilia B. A number of risk factors have been identified including duration of exposure to clotting factor, ethnicity and type of gene mutation. Patients with severe haemophilia and inhibitors generally have more orthopaedic complications and worse quality of life than those without inhibitors.²⁸ The presence of inhibitors has also been demonstrated to be associated with increased morbidity and mortality from all causes.

In patients with inhibitors compartment syndrome is just as likely but the management is more controversial and specialized. Where there are low titre antibodies, therapeutic choices to normalise clotting include higher doses of factor VIII or factor IX as well as inhibitor bypassing agents. In high titre antibody patients, options are limited to inhibitor bypassing agents, either activated prothrombin concentrated compound (FEIBA) and recombinant factor.

VIIa (NovoSeven).

There are scattered case reports and a few studies assessing factor bypassing agents in surgical patients, within which compartment syndrome is mentioned. Details of the cases are shown in Table 2 below. It is interesting to note that

Table 2 – Details of the cases. FEIBA (Factor eight inhibitor bypass activity), SSG (split skin graft), AKA (above knee amputation), rFIIa (recombinant factor VIIa).

Author	Surgery	Blood loss	Management	Outcome
Watts ²⁹	Forearm fasciotomy	Significant	FEIBA and then rFVIIa	Bled until day 3
Rajic ³⁰	AKA		rFVIIa	Bled/oozed until day 15
Negrier ³¹	Forearm amputation	No details	FEIBA 14 days	SSG later
DiMichele and Negrier ³²	Leg fasciotomy	7U, took 2 hrs	32 days FEIBA	SSG 24d later
Lauroua ³³	Forearm amputation	'Good' haemostatic control	No details	
Rangarajan ³⁴	2 forearm fasciotomies cases		rFVIIa and tranexamic acid needed	No details
Lak ³⁵	Fasciotomies x2 in same patient	Intubated/paralysed to control bleeding	FVIII and platelets for 2/52	4 week hospital stay
Moraca ³⁶	3 limb fasciotomy	No details		Successful split skin graft later
Berdel ³⁷	Forearm fasciotomy			

prolonged bleeding was associated with lower doses of bypassing agents. Little detail is however given on the timing of surgery or the initiation of bypassing agents.

Seven had a fasciotomy and where details were given (three of the seven) all had significant blood loss. In the three amputation cases, details of only two of the patients were given and they bled post-operatively for fifteen and thirty-two days.

Lauroua in 2009³³ described major and minor surgery using factor VIII inhibitor bypassing activity in patients with haemophilia A and inhibitors. The authors describe a total of 12 operations, of which seven were orthopaedic. They noticed comparable blood losses, haematoma incidence and transfusion requirements to those expected for non-coagulopathic patients undergoing similar procedures. One of their cases was an emergency forearm amputation (presumably for compartment syndrome). Details are limited but the procedure took 120 min 96 infusions of FEIBA were used lasting for 32 days. Seven units of packed red cells were required (three on the day of surgery and four on day 3). A subsequent skin graft was required 24 days later. Whilst in haematological terms the authors maintain an acceptable and successful outcome (regarding blood loss, haematoma formation and transfusion requirement), prolonged hospital stay and a significant functional handicap resulted. He concluded inhibitors were not a contraindication to surgery.

3. Conclusion

Compartment syndrome is fortunately an uncommon bleeding manifestation. It occurs when there is a critical increase in pressure within a confined osseo-fascial compartment. The subsequent decline in perfusion pressure can lead to irreversible tissue damage and cell death. The treatment is prompt surgical fasciotomy.

In PWH even trivial trauma result in an acute compartment syndrome. The clinical challenges posed are more complex and there is a risk of catastrophic bleeding. The first step in the management of ACS in PWH is to try to normalise the clotting derangement with clotting factor substitution. This can tamponade the bleeding and lower intra-compartmental pressures. The reports in the literature suggest that the majority of ACS cases in PWH will settle with clotting factor replacement and non-surgical management. If symptoms of ACS persist despite normalisation of the coagulation defect it is reasonable to measure the compartment pressure and consider surgical fasciotomy.

In PWH and inhibitors there is however significant functional and surgical morbidity associated with a fasciotomy. The decision to operate becomes much harder to justify and certainly specialist haematological input and exhaustion of non-surgical methods are mandatory. There is little published literature on the subject and those undergoing surgery had significant morbidity including prolonged bleeding and a high amputation risk. Further prospective observational studies and the use of large databases with functional as well as haematological outcomes are necessary before surgical treatment guidelines can be ascertained.

Conflicts of interest

All authors have none to declare.

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