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Original Article

Adjuvant Local Antibiotic Hydroxyapatite Bio-Composite in the management of open Gustilo Anderson IIIB fractures. **Prospective Review of 80 Patients from the Manchester Ortho-Plastic Unit**

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ABSTRACT

Background: This study aims to evaluate outcomes of using Adjuvant Local Antibiotic Hydroxyapatite Bio-Composite in management of Open Gustilo-Anderson IIIB Fractures.

Methods and results: 80 patients were managed with single-stage "Fix and Flap" along with intra-operative Adjuvant Local Antibiotic Bio-Composite. Successful fracture union was achieved in 96.1% of patients, with a limb salvage rate of 96.25%. Infection rate was only 1.25%.

Conclusion: High union rate and very low deep infection rate can be predictably achieved in complex Open Gustilo-Anderson IIIB fractures by meticulous technique, use of local adjunctive antibiotics bio-composite and a combined ortho-plastic approach.

1. Introduction

Open fractures are severe injuries, resulting from significant trauma, allowing communication between the fracture (or its haematoma) and the outer environment.[1,2] The annual incidence of open long bones fractures has been reported as 11.5 per 100,000 population.[3] Open fractures are contaminated and can threaten the limb or life, and the main goal of the management is to prevent infection and osteomyelitis.[4,5] Gustilo and Anderson classified open fracture according to the severity of soft tissue injury: ***Type I*** is a clean open fracture with less than 1 cm wound. ***Type II*** is an open fracture with 1-10 cm laceration, with moderate soft tissue damage. ***Type IIIA*** is an open fracture with more than 10 cm wound with adequate soft tissue coverage despite extensive laceration. ***Type IIIB*** is a severe form and is associated with a significant soft tissue loss of more than 10 cm that needs cover by the Plastic surgical team. While ***Type IIIC*** is an open fracture associated with arterial injury. [5] The usefulness of Gustilo Anderson classification is not only limited to evaluate the severity of soft tissue damage but also provide a prognostic value regarding complications and infection rate.[6,7] Bowen et al. reported an increase in the infection rate by 7.85 times for Gustilo Anderson III fractures compared to Type I fractures.[8] A more recent study reported that type IIIB open fractures treated with internal fixation can be associated with a 53.8% infection rate as opposed to only 7.7% infection rate in type I Gustilo-Anderson fractures.[9]

Higher rate of infections in open fractures is related to the fact that open fractures are usually associated with significant soft tissue damage, periosteal stripping and contamination.[10–12] This allows bacteria to breach the wound and to adhere to living and non-living elements such as bone and implants, producing a biofilm to protect itself.[10,13] The current philosophy for the management of severe open fractures is based on initial wound debridement, fracture stabilisation, wound closure, and systemic antibiotics.[4,13] The rate of infection has certainly decreased with the use of systemic antibiotics in patients with open fractures.[14–16] A Cochrane review conducted by Gosselin et al. had concluded that the use of systemic antibiotics for patients with open fracture was associated with a reduction in the early postoperative infection rate.[17] However, due to the nature of injury, the local tissue concentration of a systematically administered antibiotics may be low.[13] Local antibiotics however, can overcome this issue with a higher concentration of antibiotics at the surgical site, as well as avoiding any risk of systemic antibiotics toxicity.[13,18] A retrospective study of 351 open fractures conducted by Lawing et al. concluded that the rate of infection for patients with open fractures who received systemic and local antibiotics was 9.5%. This was significantly lower than the

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infection rate for those who received systemic antibiotics only (19.7%, P value: 0.011).[19]However, only 41 out of the 351 patients included by Lawing's study were of the most severe type IIIB fractures.

The risk of developing postoperative infection can vary between patients, depending on their general health and comorbidities. Host classification had been described by Bowen et al. as being useful to predict the risk of infection in patients with open fractures (**8**). Class A Hosts have no comorbidities, class B one or two comorbidities and class C with 3 or more comorbidities. Class C has a 5.72 times higher risk of having deep infection following open fractures compared to Host class A.[8]

Recent reports have suggested an improvement in limb salvage rate with Gustilo Anderson IIIB fracture when these patients are managed in a combined orthoplastic unit.[20,21] Jahangir et al. had previously published the early results from our centre for 51 patients with IIIB open fractures who underwent a single stage "fix and flap" approach with local antibiotics.[20] There was no deep infection in that series. The current study is a larger cohort with a longer follow-up period, to evaluate the incidence of deep infection, union rate, limb salvage and complications rates of a series of 80 patients who presented with Gustilo-Anderson type IIIB open fracture to our orthoplastic unit.

2. Materials and methods

A review of a prospectively collected data was conducted for all patients presenting to our orthoplastic unit with open fractures. Patients were either referred from local feeder hospitals after the initial debridement and provisional fixation or presented directly to our unit.

2.1. Inclusion criteria

All patients presenting with Gustilo-Anderson IIIB open fractures that required orthoplastic intervention were included in this study. Patients had definitive skeletal stabilisation followed by definitive soft tissue cover by a dedicated orthoplastic surgical team in a single session (fix and flap approach) with application of Cerament G bio-composite as a void filler and local antibiotic carrier.

2.2. Exclusion criteria

We excluded patients who presented with open fractures where wound closure was possible (Non IIIB) and patients who were transferred to our unit for management of complications only or for closure of fasciotomy wounds. Patients who didn't have Cerament G (as local antibiotic carrier) at the time of the definitive surgery were excluded.

2.3. Perioperative care

Systemic antibiotics were started for all patients as per the local protocol and continued until definitive wound closure. Patients without allergy to penicillin were given Co-amoxiclav (1.2 gm) IV TDS. In addition, 5 mg/kg of IV Gentamicin was administered at time of the first debridement (this was reduced to 3 mg/kg in patients with impaired renal function). Patients with allergy to penicillin were given Metronidazole, Teicoplanin and Gentamicin (dose adjusted according to their weight, age, and renal function). Multiple deep tissue and bone samples were taken at time of definitive surgery for extended culture and sensitivity as routine. All patients had Cerament G applied intraoperatively to provide adjuvant local antibiotics prophylaxis. Cerament G is Gentamicin-eluting injectable synthetic antibiotic carrier. Cerament G consists of 40 wt% hydroxyapatite particles in a Calcium sulphate matrix, containing 175 mg Gentamicin per 10 mL[22]. Cerament G has a proven ability to integrate well with bone and good radiological remodelling potential.[23,24]

2.4. Demographic data and follow-up

Pre-operative data collection included patients age, gender, site of injury and mechanism of injury. Peri-operative data included time of first debridement after injury, time of definitive "Fix and Flap" session, type of skeletal stabilisation and of soft tissue cover. Post-operative follow-up was continued until wound healing and bony union. Post-operative complications including superficial or deep infection rate, non-union incidence, Amputation rate and reoperation rate were prospectively audited and reviewed.

3. Results

3.1. Patients demographic data

Eighty patients with mean age of 41.28 (10–96) years met our inclusion criteria. There were 62 males (77.5%), and 18 females (22.5%). The mechanism of injury was road traffic accidents in 43 patients (53.75%), work related injuries in 14 (17.5%), falling from height in 14 (17.5%), blast injuries in 4 (5%), and other injuries in 5 (6.25%). Site of injury was Tibial diaphyseal in 51 patients (63.75%), ankle / distal articular tibia in 14 (17.5%), foot injury in 9 patients (11.25%), multiple fractures in 4 (5%), and femur in 2 (2.5%). Comorbidities and smoking status are summarised in Fig. 1.

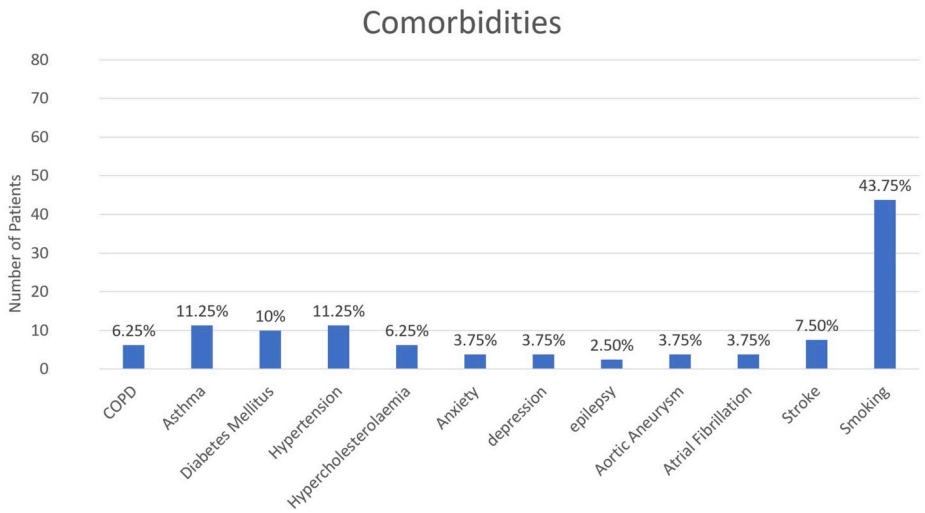

Fig. 1. Patients' comorbidities details.

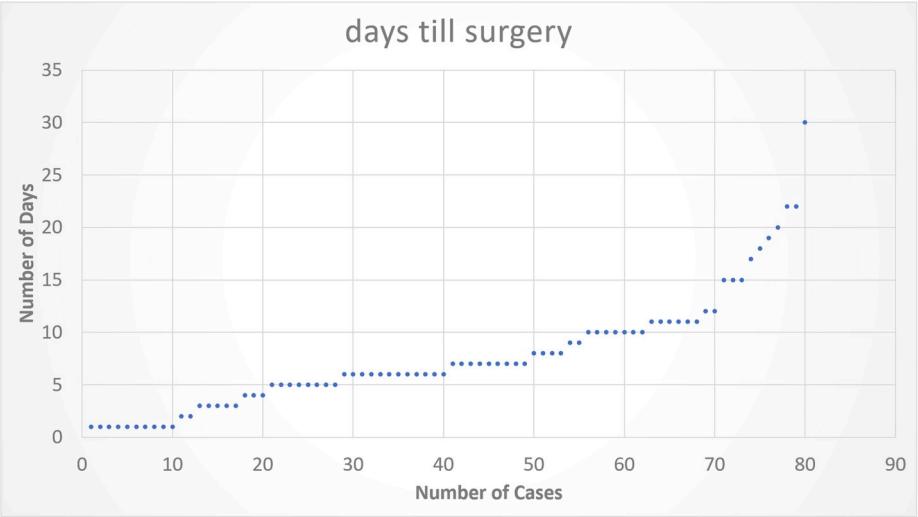

Fig. 2. A scatter chart summarising time until definitive "Fix and Flap" session.

3.2. Intraoperative orthoplastics approach

All patients had first debridement, washout and provisional skeletal stabilisation with external fixation on the next available trauma list. This was within 12 h since the time of injury in 37 patients (46.25%), and between 12 and 24 h for the remaining 43 patients (53.75%). The mean time until the first debridement since the time of injury was 11.5 h (3–22). Wounds covered with a negative pressure dressing after debridement. The mean time from injury until definitive surgery was 7.73 days (1–30 days). Seventeen patients had their definitive surgery within 72 hours from time of injury, 49 patients within 7 days of injury, 70 within 14 days and the remaining 10 patients after a delay of more than 14 days from injury (Fig. 2). This delay was either related to preoperative medical optimisation of comorbidities, delay in transfer from other local hospitals, or to the availability of combined orthoplastic expertise. Fixation method was Plate and screws in 29 patients (36.25%), Circular frame in 18 patients (22.5%), Intramedullary nailing in 16 (20%), External fixation in 5 (6.25%) and Internal fixation supported by external fixation in 3 patients (3.75%). Various methods of fracture fixation were used in the remaining 9 patients (11.25%), such as malleolar screws or Kirschner wires for fixation of metatarsal fractures. 4 patients (5%) had a significant segmental bone loss that was managed with acute shortening (up to 4 cm). Soft tissue reconstruction depended on the severity of soft tissue loss, site of injury, availability of healthy tissue for transfer and medical condition. 34 patients had Free Anterolateral Thigh (ALT) Flap (42.5%) and local/ regional flap was used in 30 patients (37.5%). Latissimus Dorsi flap used in 2 patients (2.5%), and 14 patients (17.5%) had other forms of soft tissue covering, such as split thickness skin graft.

3.3. Microbiological results at the time of the definitive surgery

Culture and sensitivity results of the deep samples taken at time of definitive surgery showed a positive growth in 31 patients (38.75%). A single pathogen isolated in 20 patients (25%), whereas 11 patients (13.75%) showed polymicrobial growth. *Staphylococcus aureus (S. aureus)*, and *Staphylococcus epidermidis (S. epidermidis)* were the most common microorganisms isolated (14 patients, 45.1%, and 5 patients, 16.12%, respectively). Samples from three patients had grown Gentamicin resistant microorganism. Two had *S. epidermidis*, and one had *S. Haemolyticus*.

3.4. Final follow-up, fracture union and limb salvage

The mean follow-up time was 22 months (9–45 months). 2 patients died within one year after surgery from conditions unrelated to injury/ surgery. Primary bone union achieved in both of them with no postoperative complications. One patient was lost for follow-up at 6 months after surgery, however, the radiographs from his last clinic review revealed evidence of progressing bony healing with no complications. This patient was excluded from calculating union rate. Amputation was required in 3patients (3.75%), resulting in a limb salvage rate of 96.25% (summarised in Table 1) .Two of these three patients required amputation within 2 weeks after surgery due to extensive soft tissue loss and flap failure, and they were excluded from calculating the union rate. Amputation was indicated in the third patient at 8 weeks following his "Fix and Flap" surgery due to flap congestion and necrosis.

Primary bone union achieved in 68 patients (88.3%) at an average of 32 weeks (17–73 weeks). Delayed union was encountered in 6 patients (7.8%), these patients had minimal radiological progression of bone healing at 38 weeks post injury. Bone healing was supplemented by injecting the fracture site with autologous Bone Marrow Aspirate Concentrate (BMAC) for these 6 patients. Subsequent follow-up confirmed successful fracture healing at 22 weeks post BMAC injection (18–26). Three patients (3.9%) had non-union as defined by the absence of any evidence of bone healing at a mean time of one year (52 weeks) after injury. All these patients had revision surgery. All of them had a circular frame, which was revised to internal fixation with autologous cancellous bone graft. Deep tissue samples for these 3 patients were negative for infection. Union was achieved in all of them by 30 weeks post revision (at 86 weeks since injury)

Table 1
Demographic data for patients who had Amputation.

	Age	Gender	Host Class	Smoker	Hours till first debridement	Days till definitive surgery
Case 1	25	Female	Class B	Yes	<12	4
Case 2	24	Male	Class A	No	<12	7
Case 3	69	Male	Class B	No	<12	5

Table 2
Postoperative complications.

Postop complication	Number (%)
Flap related complications	21 (26.25%)
Necrosis	7 (8.75%)
Congestion	6 (7.5%)
Wound Dehiscence	5 (6.25%)
Flap Failure	3 (3.75%)
Superficial Wound Infection	16 (20%)
Delayed Union	6 (7.8%)
Non-union	3 (3.9%)
Infected Metal Work	1 (1.25%)

3.5. Complications

Flap related complications reported in 21 patients (26.25%), five of them required revision plastic surgical procedure. Superficial wound infection affected 16 patients (20%). The most commonly isolated microorganism was *S. Aureus*,. These were treated successfully with antibiotics (9 patients had Initial systemic IV antibiotics followed by oral antibiotics, while 7 had only oral antibiotics). 15 patients (18.75%) needed a revision surgery (6 patients had delayed union, 3 non-union, 5 revision plastic procedures for flap related complications and 1 revision surgery for deep infection), one patient (1.25%) had infected metal work 5 months postoperatively, which required revision surgery with removal of metal work (Table 2).

4. Discussion

Type IIIB open fractures are severe injuries that usually need a multidisciplinary approach with an aim of managing soft tissues, achieving skeletal stabilisation, infection prevention, restoring limb function and rehabilitation.[20,21] These type of injuries have historically been reported to be associated with a high rate of comorbidities, deep infection rate up to 52% of patients,[9,25,26] and a 50% non-union rate.[11] However, these figures have improved in the last few years with the increased availability of the combined orthoplastic "Fix and Flap" approach as described by Gopal et al., Jahangir et al., Wordsworth et al., and Mathew et al.[4,20,21,27] Table 3 compares our outcomes in the management of Gustilo IIIB open fractures with currently published data.

4.1. Deep infection rate

Wound sepsis is one of the main complications of open fractures, Gopal et al. had reported 9.5% deep infection rate following Gustilo type IIIB open fracture. [4] Similarly, Naique et al. had reported an infection rate of 8.5% for patients with Gustilo IIIB open fractures. [25] More recently, Wordsworth et al. conducted a retrospective review showing 1.5% deep infection rate following a single stage "fix and flap" approach for management of 65 Gustilo IIIB open tibial fractures. [21] In our cohort, only one patient (1.25%) had a deep infection with a positive deep tissue sample showing *S. aureus* sensitive to Gentamicin. She was 55 years old with a history of mental health illness, type 2 diabetes, alcohol excess, smoking, recurrent pleuritis and asthma. She sustained injury when a train hit her right foot, resulting in type IIIB open fractures with extensive soft tissue loss (Fig. 3a). First debridement was performed within 12 hours of injury and the definitive Fix and Flap surgery at 3 days after injury -right foot internal fixation and free ALT flap- (Figure 3 b, c & d). She had a revision surgery at 5 months with removal of the metal work and debridement, followed by systemic antibiotics for 6 weeks. Infection was treated successfully with no signs of recurrence. This patient was Host class C, as she had more than 3 compromising factors.

Adjuvant Local antibiotics has been recommended by many authors to minimise the risk of deep infection for patients with open fractures. A systemic review and metanalysis by Craig et al. in 2014 had reported a reduction in infection rate from 31% to 9% with the introduction of local antibiotics in the management of severe Gustillo IIIB fractures. [29] High local Gentamicin levels provided by Cerament G can play a role in the prevention of biofilm formation, and its eradication. [22] In Vitro studies show Cerament G elutes Gentamicin with a high initial peak (> 4 mg/L), that remains above the minimal inhibitory concentration for Gentamicin sensitive microorganism for 28 days. [22] The systemic antibiotics concentration had been proven to remain at a safe level despite high local concentration. [22] Another advantage of using Cerament G is that the dissolution of calcium sulphate particles allows release of antibiotics leaving behind more porous hydroxyapatite scaffold, facilitating angiogenesis and new bone formation. [20] In our opinion, the low infection rate recorded in our series is likely due to the application of adjuvant local antibiotics therapy.

4.2. Fractures union and limb salvage

Primary fracture union achieved in 88.3% of patients in our series. Six patients (7.8%) had delayed union that was stimulated with BMAC to achieve union. Gopal et al. and Naique et al. had previously reported a primary union rate of 66% and 50.6%, respectively for IIIB fractures. [4,25] Jahangir et al. reported a union rate of 84.3%, and Wordsworth et al. 89.4%. [20,21] Three patients (3.9%) in our study had a non-union, and this was lower than the non-union rate reported by Wordswoth et al. (6.5%). [21]

Limb Salvage and maintaining functionality is the final aim of management of open fracture. Naique et al. and Wordsworth et al. had reported limb salvage rate of up to 94% following a combined orthoplastic approach [21,25] (Table 3). More recently, Jahangir et al. had reported a 98.1% limb salvage rate. [20] The limb salvage rate in our series was 96.25%.

A closer look at the failures highlighted that all of these patients had tibial diaphyseal IIIB fractures with significant soft tissue loss. All of them had a circular frame as the method of initial definitive fixation, and free ALT flap to cover the wound. Two patients had extensive flap necrosis, wound dehiscence and exposed tissue within the first 2 weeks, resulting in an unsalvageable limb. They had a below knee amputation. The third patient had peripheral flap necrosis and congestion at 3 weeks postoperatively. He had 2 attempted revision surgeries involving

Table 3
Gustilo Anderson IIIB Fracture outcomes from the literature.

Study	Number of patients	Follow-Up (months)	Deep Infection Rate (%)	Union Rate after the primary surgery (%)	Limb Salvage Rate (%)	Reoperation (%)
Gustilo et al. [26]	25	–	52%	–	84%	–
Gopal et al. [4]	79	–	9.5%	66%	95%	–
Naique et al. [25]	73	14	8.5%	50.6%	93%	–
Mathew et al. [27]	74	12	14.9%	–	91.9%	–
Wordsworth et al. [21]	66	40	1.5%	89.4	94%	–
Jahangir et al. [20]	51	13.9	0%	84.3%	98.1%	21.5%
Our Study	80	22	1.25%	88.3%	96.25%	18.75%

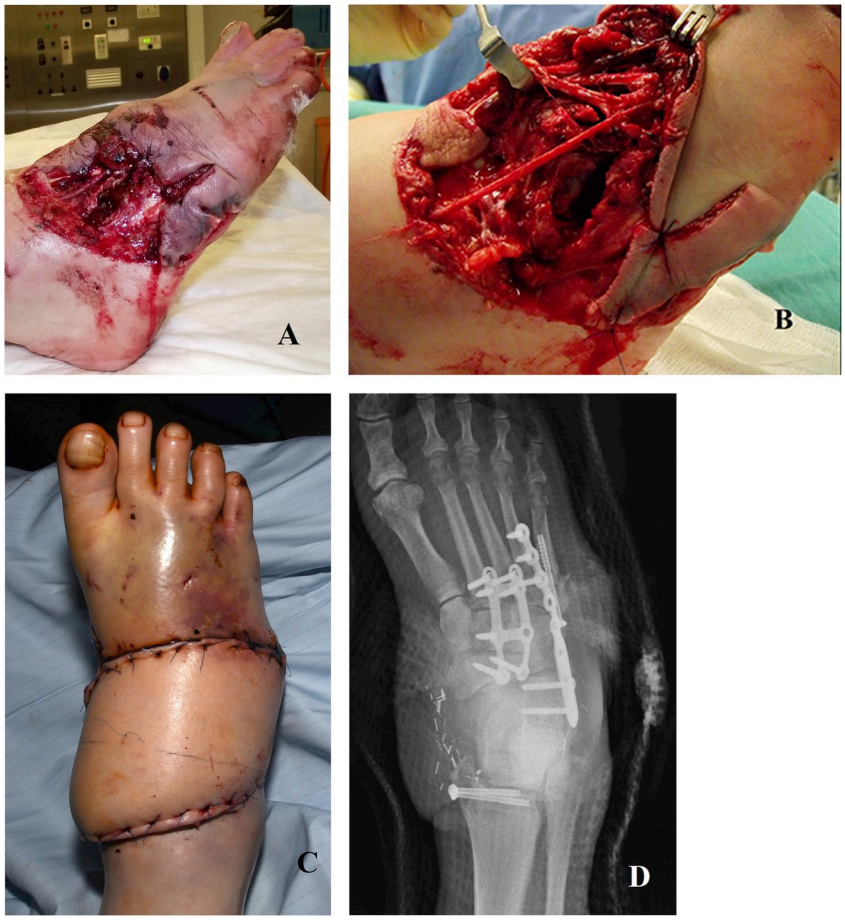

Fig. 3. Right foot Gustilo IIIB open fracture for the patient who had deep infection. A: before debridement; B: after debridement; C: 10 days post-operation; D: Postoperative XR.

debridement of necrotised tissue and application of negative pressure dressing. However, the flap failed and he needed amputation at 8 weeks following injury.

5. Conclusion

To our knowledge, this is the largest study of patients with Gustilo-Anderson type IIIB open fractures treated with a single stage orthoplastic definitive "Fix and Flap" approach from a dedicated unit. Our results highlight that low infection rates, high limb salvage rates, high union rates and low re-operation rates can be achieved in these complex injuries with a combined OrthoPlastic approach, MDT input, meticulous technique and the use of adjuvant local antibiotic bio-composite. Delay in definitive surgery, gentamicin resistance and smoking were not associated with any increased deep infection or non-union in our series. At 22 months of follow-up, deep infection rate was 1.25%, limbs salvage rate was 96.25%, fracture union rate was 96.1%, and re-operation rate 18.75%.

Disclaimer

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Authors contribution to the study

Ahmed Aljawadi: Literature review, data collection & Analysis, manuscript writing, Amirul Islam: Literature review, Data analysis, Critical review and drafting, Noman Jahangir: Literature review, Data collection & analysis, Critical review and drafting. Noman Niazi: Literature review, Data analysis, Critical review and drafting. Zak Ferguson: Data Collection & Analysis. Benjamin Sephton: Data Collection & Analysis. Mohammed Elmajee: Literature Review, Data analysis, Drafting and Critical analysis, Adam Reid: Operating surgeon, Data Collection, Jason Wong: Operating surgeon, Data Collection, Anand Pillai: Operating surgeon, Data Collection, Data analysis, Drafting and Critical analysis.

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