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Secretome – A new "Cappiler" for Compartement Syndrome

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Abstract | **Case Report**

Compartment Syndrome, an orthopedic emergency, is a condition of increased perfusion pressure under closed tissue. Necrosis of the nerves and muscles, namely contracture of Volkmann and systemic complications such as acute renal failure, sepsis, ARDS, will result in compartment syndrome that is not properly treated. In children, doctors must be able to diagnose compartment syndrome in order to treat it in a timely manner. The effects of mismanagement will have an impact on the future of the child. A 5-year-old boy presented a case report with complaints of worsening wounds accompanied by loss of sensation. As the patient went to alternative medicine, the patient had to be amputated because of an error in the administration of therapy (The patient came to the "dukun tulang" for 5 months ago and received inappropriate treatment). Patients have signed an agreement to follow up on treatment by single-dose intracutaneous injection of Placental Wharton Jelly Stem Cell Secretom (SC-PWJSC). Intracutaneous injection of Secretom from Placental Wharton Jelly Stem Cell after administration of a single dose of 5cc (SC-PWJSC). The patient was advised to undergo amputation and the SC-PWJSC intracutaneous injection procedure was given to the patient. There was a significant improvement in the situation after 4 weeks of intervention.

Keywords: Compartment Syndrome; Intracutaneous Injection, SC-PWJSC.

1. INTRODUCTION

Compartment syndrome (CS) is a life-threatening condition of the limb that can be observed when the pressure of perfusion decreases below the closed tissue. Compartment syndrome is therefore a condition in which the internal pressure in a confined space, namely a closed osteofacial compartment, increases. Reduced tissue perfusion and tissue oxygen pressure will result in increased intracompartment pressure, resulting in impaired circulation and tissue function in the room. The body will experience permanent tissue necrosis and malfunctioning when compartment syndrome is not resolved, and if it gets worse, kidney failure and death can occur [1-3].

The distal anterior lower limb in the United States is the most studied for compartment syndrome and 2-12 percent is considered the second most frequent for trauma. Compartment syndrome is more often diagnosed in males than females from the study of McQueen (2000), but this has a bias because males experience trauma injuries more often than females. McQueen examined 164 patients diagnosed with compartment syndrome, 69% associated with fractures and partially tibial fractures [4]. In 1958, Ellis reported that contractures are common in tibial fractures in 2% of ischemia. From Detmer *et al*., 82% of patients with chronic compartment syndrome have reported that bilateral compartment syndrome has occurred. Acute compartment syndrome is often caused by trauma, particularly in the lower and upper legs [4-6].

One of the orthopaedic emergencies is Compartment Syndrome (CS). To prevent a bad outcome, identifying high-risk patients, making a prompt diagnosis, and starting effective treatment are crucial steps. The failure of a doctor to communicate with children may influence a timely diagnosis of CS [7].

It can lead to necrosis of the nerves and muscles of the compartment if compartment syndrome has occurred for more than 8 hours. Severe ischemia lasting 6-8 hours can lead to muscle and nerve death, which can lead to the contracture of Volkman.

Meanwhile, in the event of multi-system organ failure, systemic complications that can result from compartment syndrome include acute renal failure, sepsis, and fatal acute respiratory distress syndrome (ARDS) [4-6].

Compartment syndrome can appear in children as opposed to in adults. The first sign of developing compartment syndrome in children is the increased need for analgesics. The inherently high risk of compartment syndrome is in children with supracondylar humerus fractures, elbow injuries, forearm fractures, and tibial fractures. Outstanding long-term results are given by proper diagnosis and treatment with fasciotomy in children [7].

A new innovative therapy concerning the role of secretome from *Placental Wharton Jelly Stem Cell (SC-PWJSC)* as a way of managing the incidence of compartment syndrome in children is discussed in this case report.

2. CASE REPORT

A 5-year-old boy has complaints of worsening wounds associated with loss of sensation (Initially severe pain). It was known that 5 months ago, the patient had a history of fractures in his left forearm and did not receive therapy from health personnel. Patients come to seek alternative medicine or what is known as 'bone dukun' in Indonesia for treatment. To prevent infection, patients have been advised to undergo amputation surgery by a surgeon. Patients visit to start alternative therapies with a single dose (5 cc) intracutaneous Placental Wharton Jelly Stem Cell Secretom injection (SC-PWJSC).

Past medical history is simply a history of untreated fractures that, from day to day, cause symptoms to worsen. Good growth and development and good children's nutrition. During the developmental period, psychosocial problems and congenital abnormalities are not present.

The present complaint is the loss of sensation, accompanied by physical examination, in the left forearm and the absence of a pulse at the end of the extremity.

Dermatological examination found multiple lesions with varying sizes ranging from 0.5 to 4 cm with crusting and signs of ischemia on the left forearm. On palpation, there is no left radial pulse (Figure 1).

Patients have signed an agreement to follow up on treatment by single-dose intracutaneous injection of Placental Wharton Jelly Stem Cell Secretom (SC-PWJSC) and routinely monitoring for two weeks. Secretom gel from Placental Wharton Jelly Stem Cell (SC-PWJSC) was also given to patients to be applied every day after cleaning the wound with NaCl. Patients are also asked to notice the side effect symptoms that may arise from allergic reactions such as itching, redness, burning sensation, and swelling in order to seek first aid if very disturbing serious side effects appear.

After three weeks of intervention with a closed wound accompanied by scarring without secondary side effects, the patient returned to control. The neovascular status of the patient also improved from the first day of the visit with the color around the bluish-red wound, but there was still anesthesia. In the absence of significant side effects, patients reported being satisfied with the development for one week. During the intervention, symptoms of side effects were not found (See Figures 2).

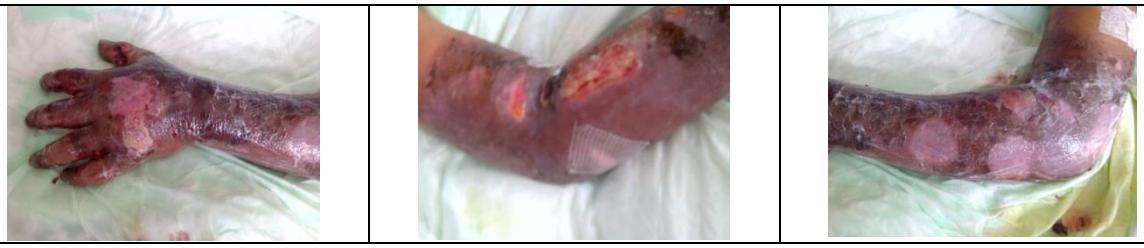

Figure 1: Compartment Syndrome in the forearm of a 5 year old child due to left untreated branchial fracture

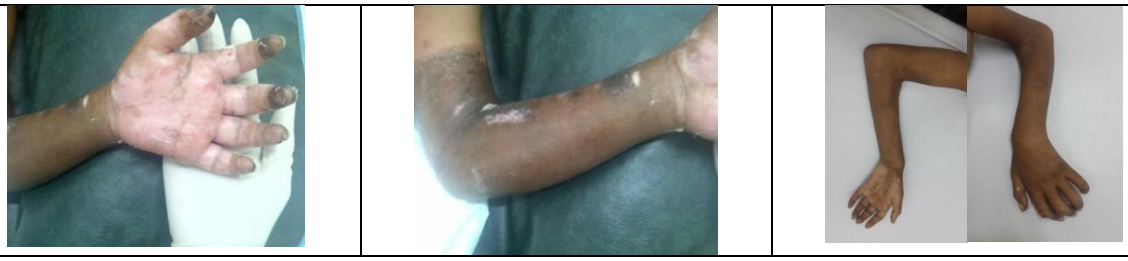

Figure 2: The success of therapy using secretom gel from Placental Wharton Jelly Stem Cell (SC-PWJSC) in Compartment Syndrome Cases

3. DISCUSSION

Compartment syndrome is a pressure increase in a compartment that results in pressure in the closed osteofacial compartment on the nerves, blood vessels and muscles. This is preceded by an increase in interstitial pressure, a lack of oxygen from blood vessel pressure, resulting in decreased tissue perfusion (ischemia) and tissue death (necrosis) [1-3]. This condition may be chronic due to muscle overdevelopment, or acute trauma and bleeding into the compartment. A medical emergency requiring immediate treatment within 12 hours is acute compartment syndrome [1-3, 8, 9].

The incidence of acute compartment syndrome is trauma-dependent. Compared to closed fractures of the tibia, DeLee and Stiehl said that 6% of open tibial fractures will lead to compartment syndrome, about 1.2% will lead to compartment syndrome. Rorabeck and Macnab reported 6 hours of successful decompression for enhanced perfusion. The results of a McQueen case study show that compartment syndrome is more frequently diagnosed in males than in females. This is because most patients suffering from trauma are male. In addition, the annual incidence of acute compartment syndrome was found to be 7.3 for males per 100,000 and 0.7 for females per 100,000. The McQueen study found that the most common cause of acute compartment syndrome is fracture. McQueen examined 164 patients diagnosed with compartment syndrome. The most common fractures in this respect were diaphysis fractures of the tibia and distal radius osteosis fractures [4-6, 8, 9].

Compartment syndrome involves normal local tissue hemostasis, leading to increased tissue pressure, decreased capillary blood flow, and hypoxia-related local tissue necrosis. The result of increased intracompartment pressure is compartment syndrome. This increase in the pressure of intracompratement depends on the event that triggered it. There are 2 types of syndrome with compartments. The first type is the acute type that is closely related to trauma, and the second is the chronic type that is usually linked to daily activities due to repetitive activities usually associated with microtrauma [1-3, 8, 9].

The fascia is a tissue that is inelastic and can not stretch, so intra-compartment pressure can be increased by swelling of the fascia and pressure on blood vessels, muscles and nerves can be caused. The swelling can result from trauma and surgery from a complex fracture or tissue injury. Routine physical activity can also cause the fascia to swell, but generally lasts only during activity [1, 2].

An ischemic injury leads to the pathophysiology of the compartment syndrome. Where there is a tolerable pressure limit within the intra-compartment structure. If the liquid increases in a fixed space, or the volume of the compartment with fixed components decreases, the pressure in that compartment will increase [1-3].

Compartment syndrome causes increased tissue pressure, decreased blood flow from capillaries, and necrosis of local tissues. Increased tissue pressure in a confined space causes venous obstruction. The continuous increase in pressure causes the lower arteriolar intra-muscular pressure to increase. At this stage, the capillary causing leakage into the compartment will not enter any more blood, which is followed by increased pressure in the compartment. Perfusion of blood through the stopped capillaries will cause tissue hypoxia. Vasoactive substances (histamine, serotonin) are released by tissue hypoxia, which increases capillary permeability, which increases fluid exudation and leads to increased pressure and greater injury. As a result, nerve conduction will be weakened, the pH of the tissue will decrease as a result of anaerobic metabolism, and the surrounding tissues will suffer severe damage. The muscles will experience necrosis and release myoglobin if it continues. Eventually, limb function is lost, threatening life in the worst case [1-3, 7].

Tissue perfusion is determined by the Capillary Perfusion Pressure (CPP) minus the interstitial pressure. Tissue perfusion is proportional to the difference between interstitial capillary perfusion pressure (CPP), expressed by the formula LBF = (PA - PV) / R, where LBF = local blood flow, PA = arterial pressure, PV = venous pressure, R = local vascular resistance. Normal cell / myocyte metabolism requires an oxygen pressure of 5-7 mmHg. This can work well with a mean CPP of 25 mmHg and an interstitial pressure of 4-6 mmHg. If the intra-compartment pressure increases, it will result in an increase in perfusion pressure as a physiological response as well as trigger an autoregulatory mechanism resulting in a 'cascade of injury' [1-3, 7].

Basically, this will increase the tissue pressure and increase venous pressure when there is fluid that enters a compartment that has a fixed volume. It will cause the arteries and muscles to collapse and lead to tissue ischemia if the interstitial pressure exceeds the CPP. The response of the body to ischemia is the release of histamine-like substances which enhance vascular permeability. In the small capillaries, this induces plasma leakage and blood clots that worsen the ischemia that occurs. Next, myocytes are lysed and myofibrillary proteins are turned into osmotic particles that actively draw water from the arteries [1-3, 7].

One milliosmole (mOsm) is estimated to have a pressure of 19.5 mmHg, so that a relatively small increase in active osmotically active particles in the closed compartment attracts enough fluid to cause a further increase in intramuscular pressure. When tissue

blood flow is further reduced, muscle ischemia and subsequent cell edema worsen [1-3, 7].

The increased tissue pressure causes venous obstruction in the confined space, regardless of the cause. The constant rise in pressure causes the lower arteriolar intramuscular pressure to rise. No more blood will enter the capillaries at this point, causing leakage into the compartment, followed by increased pressure in the intracompartment [1-3, 7].

Heavy pain will be caused by pressure on the surrounding peripheral nerves. The venous pressure rises when there is an increase in intracompartment pressure. The blood flow through the capillaries will stop after that. Oxygen delivery will also stop in this state, resulting in tissue hypoxia (pale). There will be muscle and nerve ischemia if this continues, which will cause irreversible damage (necrosis) to those components [1-3, 7].

When the pressure between continuous contractions remains high and interferes with blood flow, chronic compartment syndrome occurs. Arterial flow during muscle relaxation decreases as the pressure increases, and muscle cramps will be experienced by the patient. The anterior and lateral compartments of the lower leg are usually affected. During exercise, the muscle can expand by about 20% and will add to the temporary increase in intracompartment pressure. Intamuscular pressure can be increased by repeated muscle contractions to the extent that recurrent ischaemia may occur [1-3, 7].

The above pathophysiology explains that, as a consequence of blood flow through capillaries that stops, compartment syndrome causes tissue hypoxia. Irreversible tissue death is caused by this series of processes. In the treatment of compartment syndrome, along with the development of science and the increasing use of stem cells, innovations have been developed using secretom gel from Placental Wharton Jelly Stem Cell (SC-PWJSC)

In addition to directly implanting stem cells into the skeletal muscle, considerable focus now focuses on promoting angiogenesis to activate resident satellite cells and provide a long-lasting portal through which MDSCs can derive, ultimately to help heal the skeletal muscle. With clear evidence that exercise promotes cardiac and skeletal muscle perfusion, several studies now show this is because muscle contraction induces the formation of new vessels and the expansion of existing vascular trees, such as through voluntary exercise or neuromuscular electrical stimulation [10-12].

There are several other mechanisms, aside from promoting angiogenesis, through which exercise can improve healing. Exercise, for example, increases matrix metalloproteinase (MMP) serum concentrations that directly digest fibrotic scar tissue, regulates the secretion of pro-regenerative growth factors such as insulin-like growth factor, and can also mobilize stem cells [13-16]. In addition, several studies show that exercise-induced hypoxia promoted skeletal muscle healing by increasing hypoxia-induced factor, stromal cell derived factor and erythropoietin circulating concentrations, each of which mobilizes bone marrow endothelial progenitor stem cells to coordinate the neovascularization of hypoxic tissues [17-21]. The potential to combine MMPs and stem cells for direct implantation, as well as MMPs with conservative means of promoting angiogenesis, such as voluntary exercise and, as will be discussed below, neuromuscular electrical stimulation, certainly exists in light of this information.

Based on this data, it is possible that more traditional rest therapy may jeopardize an opportunity to locally recruit stem cells to the injury zone, at least for some instances of skeletal muscle injury. It is also possible that the activation and infiltration of stem cells into the area of injury may increase and enhance regeneration through controlled and monitored exercise regimens in appropriately selected patients, perhaps initiated prior to the completion or regeneration phase of skeletal muscle injury. Further studies may be necessary to determine whether rest is harmful to post-injury healing, whether certain exercises are safe and clinically beneficial, and, if so, whether the timing of rehabilitation of exercise relative to the onset of injury affects outcomes [22].

As with exercise, neuromuscular electrical stimulation is another modality that seems to promote angiogenesis and skeletal muscle healing after injury (NMES). While there is a lack of data linking stem cell activation and recruitment to NMES, there is evidence that angiogenesis is promoted by this modality. As with exercise, NMES-induced tissue hypoxia may play a role in promoting angiogenesis, although the exact mechanism requires further elucidation [23, 24]. Quintero has shown that NMES significantly increases the percent capillary area of the anterior tibialis (unpublished data) among 9-week-old male C57BL/10J mice, prophylactic and post-injury NMES. In addition, the percentage of regeneration significantly increases at 5 and 10 days after injury and the percentage of fibrosis decreases significantly along the injury zone in mice undergoing prophylene prophylaxis (unpublished data) [22].

One reason why prophylactic NMES may be superior to post-injury stimulation is that, in the presence of more MDSCs derived from the vascular endothelium, as well as more infiltrating growth factors that activate dormant satellite cells, the regenerative stage of skeletal muscle injury will begin to occur by promoting angiogenesis early on. With post-injury

stimulation, these cells and factors may enter the injury zone beyond the optimal tissue repair time window. While speculative on our part at the present time, this would be consistent with our above proposal that in some cases of skeletal muscle injury, early exercise rehabilitation programs may be beneficial, although clinical studies are necessary to support this. This may also be similar to the fracture repair process in which relatively early fracture stabilization is often required to prevent progression to non-union fracture [25].

4. CONCLUSION AND SUGGESTION

Compartment Syndrome is a condition where the perfusion pressure increases under closed tissue is an orthopedic emergency. Compartment syndrome that is not treated properly will result in necrosis of nerves and muscles. In the case study, it was found that a 5-year-old boy patient presented with complaints of worsening wounds accompanied by loss of sensation, which was caused by errors in administering therapy (seeing a bone healer or alternative medicine). The patient was advised to undergo amputation by the surgeon, but the patient was given alternative therapy in the form of 5 cc single dose intracutaneous secretom injection from Placental Wharton Jelly Stem Cell (SC-PWJSC). Four weeks after being given the SC-PWJSC intervention, there was a significant improvement in the condition without any side effects.

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