PEDIATRIC SURGERY *Update**
Vol. 55 No. 04 OCTOBER 2020

Sirolimus for Lymphatic Malformations

Vascular malformations consist of congenital anomalies that can involve four types of vessels (capillary, lymphatic, venous and arterial). They are further subdivided in low- or high-flow vascular malformation. Lymphatic malformations are rare low-flow congenital vascular malformation occurring due to abnormal embryologic development of lymphatic vessels classified as macrocystic, microcystic or combined. Treatment frequently includes surgical excision and debridement, laser, sclerotherapy and embolization. Growth and expansion of vascular/lymphatic malformations cause disfigurement, chronic pain, recurrent infections, coagulopathies, organ dysfunction and death. Sirolimus, also known as rapamycin, is an mTOR inhibitor. mTOR is a serine/threonine kinase that acts as a master switch in cell proliferation, apoptosis, metabolism and angio/lymphangiogenesis. Sirolimus inhibit directly the mTOR pathway which inhibits cell proliferation, angiogenesis and lymphangiogenesis. It is used to prevent rejection of kidney transplants. The overall success rate of sirolimus in vascular and lymphatic malformation is 80%, presenting as improvement in radiologic imaging and reduction in symptoms at a median time of 10 weeks, with a reported nonspecific decrease in lesion size. In hepatic hemangioendothelioma with life-threatening Kasabach-Merritt syndrome, sirolimus is associated with resolution of coagulopathy in 93% of patients in two weeks period. In lymphatic anomalies oral sirolimus is associated with clinical benefit in 95% of patients with decrease of lesion size. Clinical improvement is observed in 75% of patients after three weeks of therapy. Dose most often prescribed is 0.8 mg/square meters twice daily in the pediatric patient. The more favorable response to sirolimus is seen in young patients less than two years old suggesting therapy should be started early in life. Mainly low-flow lesions, overgrowth syndromes with low-flow components and vascular anomalies that demonstrate upregulation of the mTOR pathway respond to sirolimus in most cases probably due to inhibition of lymphatic expansion and soft-tissue overgrowth. Topical use of sirolimus in cases of skin malformations with lymphatic components such as congenital lymphatic-venous malformations is both efficient and safe. Side effects of oral sirolimus include oral mucositis, fatigue, headaches, hypertension, thrombocytopenia, leucopenia, anemia, hyperlipidemia, hyperglycemia, hypokalemia, increase liver enzymes and rash. Side effects after sirolimus therapy are manageable, with no effect in future growth and development.

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Thoracoscopic Repair of CDH

Congenital diaphragmatic hernia (CDH) is a defect caused by incomplete closure of the fetal posterolateral diaphragm muscle during embryonic development with entry of abdominal organs into the thoracic cavity resulting in lung hypoplasia. The defect is easy to repair with primary closure or patch replacement through a transabdominal subcostal incision or thoracotomy. The former is preferred in order to rearrange the hernia content into the abdomen. Patch repair has a significant higher recurrence rate than primary closure. The prognosis of CDH is primarily determined by the degree of persistent pulmonary hypertension and pulmonary hypoplasia. Surgical readiness for CDH repair implies that urine output is > 1 ml/kg/hr, lactate is < 3 mmol/L, FiO2 < 0.5, normal blood pressure and pulmonary pressure less than systemic pressure. Minimally invasive techniques using both laparoscopy and thoracoscopy have recently been implemented for repair of CDH. Advantages of the thoracoscopic approach include less pain, less incisional complications along with a reduction in surgical stress. Some surgeons are reluctant to do a thoracoscopic approach as malrotation cannot be managed adequately, though the incidence of acute volvulus is very low. Contraindications for thoracoscopy in CDH include babies using ECMO therapy. Thoracoscopy is not contraindicated in newborns as a relative hypercapnia can be tolerated without adverse effect in terms of neurological development. With low insufflation pressures (4-7 mmHg), CDH patients have significant improved hypercapnia and acidosis. Large defects and defects unable to reduce the herniated intrathoracic abdominal organs are reason for conversion. Use of patches to close larger diaphragmatic defects is instigated by the high percentage of recurrence (33%) in the thoracoscopic primary repair group. The liberal use of patches to reconstruct the dome of the diaphragm has reduced the incidence of recurrence to 12%. The recurrence rate is higher for thoracoscopy repair than primary repair. Factors associated with recurrence included the nature of the defect (large, right, absence of peripheral rim), associated conditions (severe pulmonary hypertension) and the surgical approach (use of patch, minimally invasive approach). The surgical postoperative mortality between the open and thoracoscopic approach favors the later but is non-concluding since patients with less severe disease or with late presentation that have better survival (less lung hypoplasia) are better candidates for the minimal invasive approach. Also patch repair is associated with higher mortality given these patients are more likely in ECMO, presents with liver herniation

and absent peripheral rim. Use of biologic mesh underlay appears to confer a reduced hernia recurrence.

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Intraoperative Temperature and SSI

Perioperative temperature regulation during surgery in children can be a determinant of several factors including surgical site infections (SSI). Surgical site infections are the third leading cause of nosocomial infections among surgical patients. SSI is a major cause of postoperative morbidity also associated with increased risk of mortality. SSI increases surgical stay and hospital costs. Measures to prevent SSI includes use of prophylactic preoperative antibiotics, use of hair clippers, appropriate surgical field preparation and avoidance of postoperative hyperglycemia. Intraoperative hypothermia defined as core temperature < 36.0 C during surgery is a common complication among surgical patients. Hypothermia triggers thermo-regulatory vasoconstriction, moving the Bohr curve toward the left and decreasing the partial pressure of oxygen in tissues, leading to local acidosis. It also impairs oxidative killing by neutrophils, interferes with collagen deposition resulting in impaired wound healing. Infants are more susceptible to temperature instability owing to their immature thermoregulatory systems and increased exposed surface to volume ratio. Hyperthermia is defined as a temperature above 38 grade C. SSI has not been demonstrated to increase with intraoperative and/or immediate postoperative hypothermia in children. On the other side, hyperthermia at any point during the case or immediately postoperatively is associated with higher odds of developing SSI within 30 days of surgery. Babies undergoing laparotomy for necrotizing enterocolitis who have a precipitous drop in intraoperative temperature have no increased in SSI development. In fact, controlled hypothermia in NEC cases may be advantageous similar to its use in hypoxic ischemic encephalopathy, severe liver failure and other conditions. Hypothermia indices a regulation of immune response with decrease oxidative stress and decrease leukocyte accumulation that help to explain this `protective' effect. On the other side, hypothermia causes

deleterious effects such as coagulation disturbances, hypotension and unreliable action of anesthetic agents with more respiratory, thermoregulatory and cardiovascular intervention needed for stabilization. Risk factor for hypothermia in surgical patients include colder ambient temperature and longer case length. Blood transfusions given preop, intraoperatively and within 72 hours of surgery are associated with development of SSI. After reviewing several series, intraoperative hypothermia is not significantly associated with SSI.

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**** PSU 1993-2020***
ISSN 1089-7739