orphanaesthesia

Anaesthesia recommendations for patients suffering from

Harlequin ichthyosis

Disease name: Harlequin ichthyosis

ICD 10: Q80.4

Synonyms: Harlequin baby, ichthyosis congenita, Ichthyosis fetalis, keratosis diffusa fetalis, Harlequin fetus, Ichthyosis congenita gravior

Disease summary: Harlequin ichthyosis (HI) is an autosomal recessive congenital ichthyosis. HI is an extremely rare and most severe form of ichthyosis. The condition is caused by mutation of the *ABCA12* gene resulting in impaired lipid transport in the outermost layer of the skin, the epidermis. During the neontatal period, harlequin ichthyosis manifests phenotypically as dramatic large polygonal plate-like scaling of the skin that cracks and can slough, revealing the underlying diffusely bright red skin. These thick skin plates can pull and distort facial features. The tightness of the skin can also pull on the eyes and mouth resulting in difficulties with closing these structures. The tightness also causes the eyes and the mouth to turn inside out resulting in ectropion and eclabium. Other features include hypoplasia of the fingers, malformation of the ears and nose, and alopecia. Affected neonates often do not survive and mortality is commonly attributed to respiratory failure and/or sepsis. Clinical data obtained from 45 HI patients revealed 25 survivors and 20 deaths with an overall survival rate of only 56%. The ages of survivors ranged from 10 months to 25 years and death usually occurred in the first 3 months. HI infants need to be cared for in a neonatal intensive care unit immediately after birth. Several harlequin neonates have survived. They tend to have severe erythroderma and fine scaling, even with optimal management. Survivors can suffer from recurrent skin infections from epidermal fissuring, contractures due to their tight skin, metabolic abnormalities, developmental delay, and pulmonary issues. High quality management of immediate newborn care may improve survival. Introduction of oral retinoids and its timing remain controversial, but frequent application of emollients to improve barrier function is critical.

Medicine in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

Based on the limited data available, HI patients are not limited to any specific surgical procedure. Because of its extremely low prevalence, the evidence of such surgical cases is very rare and they call for interesting case reports.

Type of anaesthesia

Based on the limited data available, HI has no contraindications to general, MAC, regional or neuraxial anaesthesia type but there are no definite specific recommendations for either. The type of anaesthesia should be tailored for individual patient based on their age, co-existing problems, and the risk of surgery.

Necessary additional diagnostic procedures (preoperative)

In HI patients, the disorder initially mainly effects the skin. Their diagnosis, if unknown prior to surgery, can be initially made by physical exam only since HI patients have very distinctive features. Phenotypically, HI manifests as very hard, thick skin that covers most of patient's body. The skin has large, diamond shaped plates that are separated by deep fissures. This effects the shape of eyelids, nose, mouth, and ears, and causes restricted movement of the arms and legs. The restricted movement of the eyelids, mouth, chest and the extremities may lead to breathing difficulties, poor oral intake, and dry or damaged cornea. The skin abnormality associated with the HI disrupts the normal skin function and causes problems with water loss control leading to dehydration and hypernatremia, regulating the body temperature, and sepsis. These patients have to be carefully evaluated by physical exam and the laboratory studies to assess the degree of dehydration, electrolyte disturbance, active infections, malnutrition, eye injuries, xerostomia, and any other abnormalities.

HI is an autosomal recessive disorder caused by mutation of the *ABCA12* gene resulting in impared lipid transport. A loss of functional ABCA12 gene protein causes abnormal development of the epidermis, resulting in thick, hard, scaly skin characteristic of HI. Identification of this gene has made the definite diagnosis possible. This mutation can be confirmed by a blood test processed by specialized laboratories where they look for specific mutations in the ABCA12 gene. Some mutations in this gene prevent the cell from making any protein while other mutations lead to production of a very small amount of the protein. The degree of mutation effects the amount of protein generated by the cell thus effecting the lipid transport which can range from none to very minimal and extremely impaired. Because the test may take days to weeks for processing, the sample needs to be sent out much in advance of the scheduled procedure if the diagnosis needs to be made or confirmed. This test provides >95% sensitivity for the diagnosis of HI.

Particular preparation for airway management

For difficult airway please follow the Difficult Airway algorythm. For other cases, some adjustments may be necessary.

Although there are limited data on exact airway managment in HI patient population, their physical characteristics due to HI disease may pose some challenges during intubation.

The hyperkeratosis of the skin overlying the neck may lead to limited neck mobility necessary for mask vantilation and intubation. In addition, the hyperkeratosis may lead to limited mouth opening for intubation. It is extremely important to perform a very detailed airway exam including MP score, thyro-mental distance, and neck mobility. Xerostomia seen in some of HI patients may cause mucosal damage and tear during direct laryngoscopy and passage of the ETT. Since the use of GlideScope may help visualize the vocal cords in patients with limited neck mobility and with restricted mouth opening, it's use can be justified in HI patients. In addition, lubricating the GlideScope blade and the ETT with the sterile water soluable lubricating jelly may minimize risk of trauma to the oral cavity from xerostomia.

The hyperkeratotic, emollient-covered skin seen in HI patients makes it difficult for any tape to adhere. Thus, taping and securing the ETT may be a huge challenge. Here are some ways by which the ETT can be secured in this patient population: Hollister skin gel, any ICU/respiratory therapy unit approved tube holder that does not require adherence to the skin, and umbilical ties.

Is important to lubricate the lips prior to masking and/or intubating these patients. The proper lubrication will prevent additional skin trauma during the airway management.

Particular preparation for transfusion or administration of blood products

Based on the limited data available, there is no evidence of platelet function deficiency, abnormal red blood cell counts, and altered coagulation or impaired vessel reactivity in this patient population. Therefore, there is no particular preparation for transfusion or administration of blood products. Normal transfusion standards and universal guidelines should be followed.

Particular preparation for anticoagulation

Based on the limited data available, there is no evidence that supports increased coagulation in this patient's population and there is no evidence to support any need for particular anticoagulation therapy.

Particular precautions for positioning, transport or mobilisation

The hyperkeratosis of the skin overlying the patients body may cause restricted movement of the arms, legs, and limited flexion of the neck. The patients transport and positioning to and from the operating room table has to be performed delicately as the epidermis is prone to cracking, increasing infection risk.

Careful movement of the patient's lower extremities, extra support (cushions, pillows) under their neck, and avoidance of any abrasions during the transport is strongly recommended.

Probable interaction between anaesthetic agents and patient's long-term medication

Enhanced survival and decreased morbidity in HI patients is reported with the use of systemic retinoids. They bind to specific retinoic acid receptors to regulate gene transcription. They influence keratinocyte differentiation, normalize abnormal keratinocyte proliferation, and mediate desquamation of hyperkeratotic scale. Frequent application of emollients is recommended to ease this shedding of thick plates while on retinoid therapy.
Etretinate was first used for the treatment of this disorder in 1985. An effective dose of 1mg/kg/d was established. Etretinate is no longer available due to its serious side effects, but it has been replaced by other retinoids with improved safety profiles. Some examples of currently used retinoids for HI are Acitretin and Isotretinoin.

Acitretin is a carboxylic acid derivative of etretinate and is most commonly prescribed in neonates with HI. Initial doses of 0.5 mg/kg/d are recommended. Improvement in hyperkeratosis, ectropion, and eclabium are reported.

Isotretinoin is another agent used in HI patients. The reported dose is 0.5 mg/kg/d. Treatment is usually initiated within the first few days of life and given orally. Case reports have documented improvement in pliability of the skin, limb movements, sucking, and eyelid closing within a week of starting therapy. Treatment has been continued for several years in some patients, and it may be required indefinitely to prevent relapse.

Retinoids may have adverse effects on liver and skeletal muscles. Liver function and serum lipid levels should be obtained prior to retinoid treatment start and should be monitored during retinoid therapy. Clinical monitoring for skeletal adverse effects should be done periodically. If retinoid treatment leads to significant liver dysfunction this may call for eliminating the use of certain anesthetic agents in this patient population that depend on liver metabolism or clearance.

Anaesthesiologic procedure

Based on the limited data available on conducting general or neuraxial anaesthesia in HI patient population, there has been no reported complications with the use of opioids, sedatives, muscles relaxants (both depolarizing and non-depolarizing), and/or local anaesthetic medications.

There have been reports of successful general anaesthesia. There also has been a case report of successful use of epidural/spinal in only known parturient with the diagnosis of HI.

Particular or additional monitoring

Standard anaesthesia monitoring is recommended for any surgical procedure which should include ECG, BP, Pulse oximetry, temperature, and end-tidal CO2.

If high-risk surgery, major fluid shift, and/or advanced disease then placement of invasive monitors such as arterial line and central venous line is recommended. In case of cardiomyopathy, transesophageal echocardiography may be useful.

When placing any non-invasive or invasive monitors, the primary obstacle is working with the skin abnormality. Fragile skin, use of emollients, and constant skin flaking prevents using of

adhesive tape to secure anything to patients skin. Anesthesiologists should be equipped with extra gauze rolls and be prepared to use this as the alternative to adhesives. Avoidance of any chemical adhesives is recommended to prevent skin damage when removing secured objects.

Placement of the PIV may not be difficult but securing it to the flacking emmolient covered skin can be very challenging. This may be solved by securing the PIV using gauze wrapped circumferentially around the catheter. The same problem exists when trying to secure arterial line or epidural catheter. Epidural catheter may be secured with a crepe bandage circumferentially wrapped around the abdomen and over the shoulder.

In the operating room, electrocardiogram (ECG) and electrocautery ground pads may fail to adhere due to combination of scaly skin and use of emmolients. This may be overcome by placing extra lubricant under the ECG pads to maximize skin contact and securing the pads with gauze wrap to prevent displacement. ECG conduction should be appropreate. The non-invasive blood pressure cuff may be applied with gauze wrapped loosely under the cuff for cushioning. Cycling may be reduced to every 5 minutes to minimize any skin trauma induced by usual placement and cycling.

Additionally, due to concerns about compromised skin causing impaired thermoregulation, the use of forced-air warming blankets is recommended to prevent potential hypothermia.

Possible complications

Harlequin ichthyosis is a rare, severe form of congenital ichthyosis associated with high morbidity and mortality. Survival rate is very low due to sepsis and/or respiratory failure.

The armor-like covering restricts patients movement and results in deformities of the face, head and extremeties. As the skin barrier is severely compromised, these patients are prone to sepsis, dehydration, and impaired thermoregulation. These patients have ectropion and eclabium, and the nose and ears are flattened.

The primary obstacle is the skin abnormality. Even the most basic procedures (patient transport and positioning) has to be performed delicately as the epidermis is prone to cracking, increasing infection risk. Fragile skin, use of emollients, and constant skin flaking prevents use of adhesive tape to secure anything to patients skin. Anesthesiologists should be equipped with extra gauze rolls and be prepared to use this as the alternative to adhesives. This becomes important when securing ECG pads, endotracheal tubes, peripheral IV's, arterial lines, cenral venous lines, and any additional catheters such as epidural catheter.

Thick skin plates seen in HI patients can pull and distort facial features. This tightness can pull on the eyes and mouth causing them to turn inside out and resulting in difficulties with closing them. This constriction of the mouth or inability to close the mouth can interfere with sucking mechanism in newborns and may require a feeding tube placement for nutrition. Hyperkeratosis overlying the neck may restrict the neck movement leading to difficulty with intubation. Once the airway is obtained, difficulties with fixating the ETT have been reported.

Ectropion and eyelid contracture characteristic of HI prevents these patients from closing their eyes at all times. Normally HI patients keep their eyes manually lubricated constantly. Eye protection during general anesthesia may be accomplished by applying eye lubricant and using corneal shields.

HI infants need to be cared in neonatal intensive care. Early introduction of oral retinoids and emollients, and high quality of immediate newborn care may improve survival.

Postoperative care

Degree of postoperative monitoring and care depends on patient's preoperative condition and the surgical procedure. HI patient emollient and/or retinoid home therapy should be continued as soon as possible.

Information about emergency-like situations / Differential diagnostics

Disease triggered emergency-like situations have not been studied or reported in this patient population.

Ambulatory anaesthesia

There is no ambulatory anaesthesia data in HI patient population. Due to its low prevalence, there have been no studies performed on complications from specific procedures, treatment, or medications. If possible it is recommended to avoid ambulatory anaesthesia. However, this decision can be left to the discretion of the team caring for the patient based on patient's age, coexisting problems, and the risk of surgery.

Obstetrical anaesthesia

Due to rarity of the disease and very low rate of survival into adulthood, there is only one case report of pregnancy in HI patient followed by birth of a healthy neonate. In this case report both general and neuraxial anaesthesia were conducted successfully. The case describes in detail all the challenges that anesthesiologist had to overcome due to patients skin condition.

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Please note that this guideline has not been reviewed by an anaesthesiologist but by two disease experts instead.