Original Research Article

Anaesthetic Implications of children with Larsen syndrome

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Abstract

Objectives: Larsen Syndrome (LRS) is a rare osteochondrodysplasia, presenting with large-joint dislocations, foot deformities and craniofacial abnormalities. These often require early and multiple orthopaedic interventions to maintain age appropriate function which necessitate repeated anaesthesia. Other than the skeletal deformities, this syndrome is also associated with other multisystem (cardiac, spinal, respiratory) involvement, a thorough knowledge of which is essential to optimise perioperative outcomes. We analysed the clinical data in our cohort of children with LRS undergoing orthopaedic intervention and detail the anaesthetic management in these children. The commonest problems involved the airway and cervical spine and these required proactive management. The primary objective is to note the anaesthetic challenges for children affected with Larsen Syndrome.

Materials and Methods: This retrospective study done at a tertiary care centre, includes, all children or families with Larsen syndrome who had been identified in the paediatric orthopaedic clinic from January 2005 to December 2015. After acquiring Institution ethics committee approval, data was collected from the hospital registry for all cases. Anaesthesia protocol was observed in the perioperative period. Difficult airway and cervical neck instability were noted and management discussed. Statistical analysis was not required.

Results: There were ten children from ten families diagnosed with LRS. Systemic and skeletal anomalies were noted.

Conclusion: Larsen syndrome is a well-known entity, even amongst the Indian race. Carefully management in the entire perioperative care, is required for safer outcomes, reduced length of stay in the hospital and improved patient and provider satisfaction.

Introduction

The NORD (National Organization for Rare Disorders), describes Larsen Syndrome as a rare genetic disorder with a wide range of symptoms, affecting both sexes. In the general population the estimated incidence is 1 in 100,000 individuals. The diagnosis is difficult, however, newer molecular genetic testing makes it possible to diagnose and treat early, in addition to clinical and radiological findings. Multidisciplinary approach is required, with good planning. This study presents the management of ten cases. One is very likely to come across these patients and need to be aware of all the challenges. This article will certainly help give an over view. Children with Larsen Syndrome pose anaesthetic challenges which need to be addressed with introduction of newer equipment and evidence to ensure safe and scientific methods of management, such as, screening tests prenatally and preoperatively, use of videolarygoscopy for difficult airway, when there is cervical spine instability. Most of these children, come for several surgeries, have coexisting congenital heart conditions and warranting ICU admission. At most care of these patients in the entire perioperative period is of paramount importance. The experiences in the management of these patients are well described in this study.

Larsen syndrome is one of the chondrodysplasia syndromes associated with abnormal bone, connective tissue and cartilage growth. Larsen, Schottstaedt and Bost in 1950 described a syndrome of multiple congenital orthopaedic anomalies (dislocations, clubfoot, finger anomalies) associated with abnormal facies (prominent forehead, depressed nasal bridge, wide-spaced eyes) named the Larsen Syndrome (LRS).[2] It has a reported incidence of about 1 in 100,000 live births. The phenotype-gene relationships is that, it's an inherited autosomal dominant disorder, cause being, Filamin B gene (FLNB) located at 3p14.3, occuring due to mutation in the phenotype.[3] This study is aimed to look at the preoperative planning and safety of anaesthesia management when these children undergo surgery.

Materials and Methods

This is a retrospective cohort study including all children or families with Larsen Syndrome, who had been identified in

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the paediatric orthopaedic clinic from January 2005 to December 2015. After acquiring Institution ethics committee approval, data was collected from the hospital registry for all cases and a retrospective chart review was performed. Diagnosis was clinical and based on the criteria described by Rodriguez et al.[5]

The clinical and radiological features relating to hyperlaxity based on Ruth Wynne Davis criteria,[6] spine, bone and joint abnormalities, craniofacial features, pulmonary, cardiac findings and pedigree information, were noted from the case sheet and preanaesthetic records, to confirm the diagnosis. Children suspected to have Larsen's were assessed by the Neurosurgery team preoperatively for spinal instability. Atlantoaxial dislocation (AAD) or instability was ruled out in all. However, all children with cervical spinal abnormalities were considered to have a potentially difficult airway due to anticipated problems in positioning and associated laryngeal malformation.

Positioning was achieved with care to secure manual cervical in-line spinal stabilization. Sand bags or the posterior part of a hard cervical collar is kept in place to minimize movement. Fitness was granted after obtaining informed consent, fasting orders and pre-medication given. The children with no anticipated airway compromise, were premedicated with oral trichloryl syrup (75-100mg/kg), one hour prior to shifting to the operating room. Results of the clinical spectrum, operative plan, radiological and laboratory investigations were noted. The details of the anaesthetic plan, surgical procedures, periprocedural course and outcomes were also analysed.

Anaesthesia Protocol

Overall general principles of paediatric anaesthesia were followed. However, only the anaesthetic implication of airway, cervical spine instability and pain management are highlighted and discussed in this article.

Routine cockpit check of the anaesthesia machine, equipment and drugs was performed. The child was positioned gently on the operating table, with care of the cervical spine, of paramount importance, especially while shifting. Standard non-invasive monitors (automated non-invasive blood pressure, ECG, Pulse Oximeter) were placed. Induction was performed by tidal breathing of sevoflurane 4-7% with 100% oxygen. Neck extension was avoided during mask ventilation, and no difficulty in ventilation was encountered. If necessary, a proper oral airway ensures adequacy of the upper airway and enables ventilation of the lungs. The airway used to prevent the tongue from falling back once the child is asleep may need to be of a larger size than indicated for a child of that age. An intravenous access was attained during this time. To facilitate intubation, muscle relaxants, like depolarizing agent suxamethonium (1-2 mgs/kg) or non-depolarizing agent, atracurium (0.5 mg/kg), was given only after confirmation of adequate mask

ventilation. For most cases, with unanticipated difficult airway, surgery lasting less than 120 minutes, once adequate depth of anaesthesia was achieved, the airway was secured with an appropriate size Classic or Proseal LMA. However, for anticipated difficult airway cases, the airway was secured with either a fibro-optic bronchoscope or video laryngoscope. Intravenous dexamethasone (0.1mg/kg) was given, if there was a difficult airway manipulation encountered. A caudal block was performed, for lower limb surgery, in the left lateral decubitus position with 1ml/kg of 0.25% bupivacaine with using a 23G hypodermic needle. Intravenous paracetamol (15-20 mg/kg) was administered in addition to fentanyl (1-2 ug/kg or morphine 0.05-0.1mg/kg), as part of the multimodal approach for analgesia. The neck remained in a neutral position when the child was turned in the lateral position, during the procedure and getting back to supine the position, as aided by the skilled assistant. Anaesthesia was maintained with isoflurane (MAC of 0.8-1%) and a mixture of 40% oxygen and air with atracurium, the muscle relaxant, given only after confirming easy mask ventilation and securing the airway. The most patients remained comfortable and hemodynamically stable during the surgery that lasted for about 90 min. Postoperative course remained uneventful. There was no nausea, vomiting, pruritus or urinary retention and pain was under control with 6th hourly paracetamol only until discharge. Difficult airway cases were not extubated immediately but electively in the ICU, which was a safer option, to avoid tight laryngospasm, difficult reintubation, rapid desaturation and subsequent adverse events.

Results

There were ten children from ten families diagnosed with LRS. Male and female involvement was almost equal in this cohort. Table 1, shows the clinical presentations. Surgical intervention as per requirement- Open reduction both hips, physeal bar release, ACL reconstruction, Ilizarov assisted correction of knees, supramalleolar osteotomy, V-Y Quadricepsplasty. However, none needed any spine correction. The major anaesthetic concerns can be largely classified into management of the airway and spinal anomalies. Secondary problems like pulmonary dysfunction and cardiac anomalies are the other problems encountered. Hypoplastic anterior part of cervical vertebrae causing cervical kyphosis, absence of cartilages in the larynx, infolding arytenoids, tracheal stenosis, absent epiglottis and arytenoids, these factors leading to difficult airway management.

Clinically, there was no evidence of any cardiac defect and electro-cardiogram (ECG) and two-dimensional echo were normal for all cases.

Table 1

| *Skeletal anomalies*	**Number of cases (Out of 10)**	*Systemic anomalies*	**Number of cases (Out of 10)**
Congenital foot deformities (equinovarus or equinovalgus)	5	Cleft lip and palate	1
Dislocations of the hip, knee, elbow and shoulder	8	Hearing loss (malformed ossicles)	2
Short stature	0	Laryngotracheomalacia, cardiac anomalies	2
Spinal deformities (scoliosis, cervical kyphosis, atlantoaxial instability, vertebral fusion, dysraphism, cervical myelopathy)	4	Missing epiglottis and arytenoids	1
Abnormalities of phalanges (spatulate fingers, pseudoclubbing, supernumerary carpal and tarsal bone ossification centres)	3	Distinctive "dish-like" craniofacies (prominent forehead, micrognathia, hypertelorism, flattenned nasal bridge, malar flattening)	5
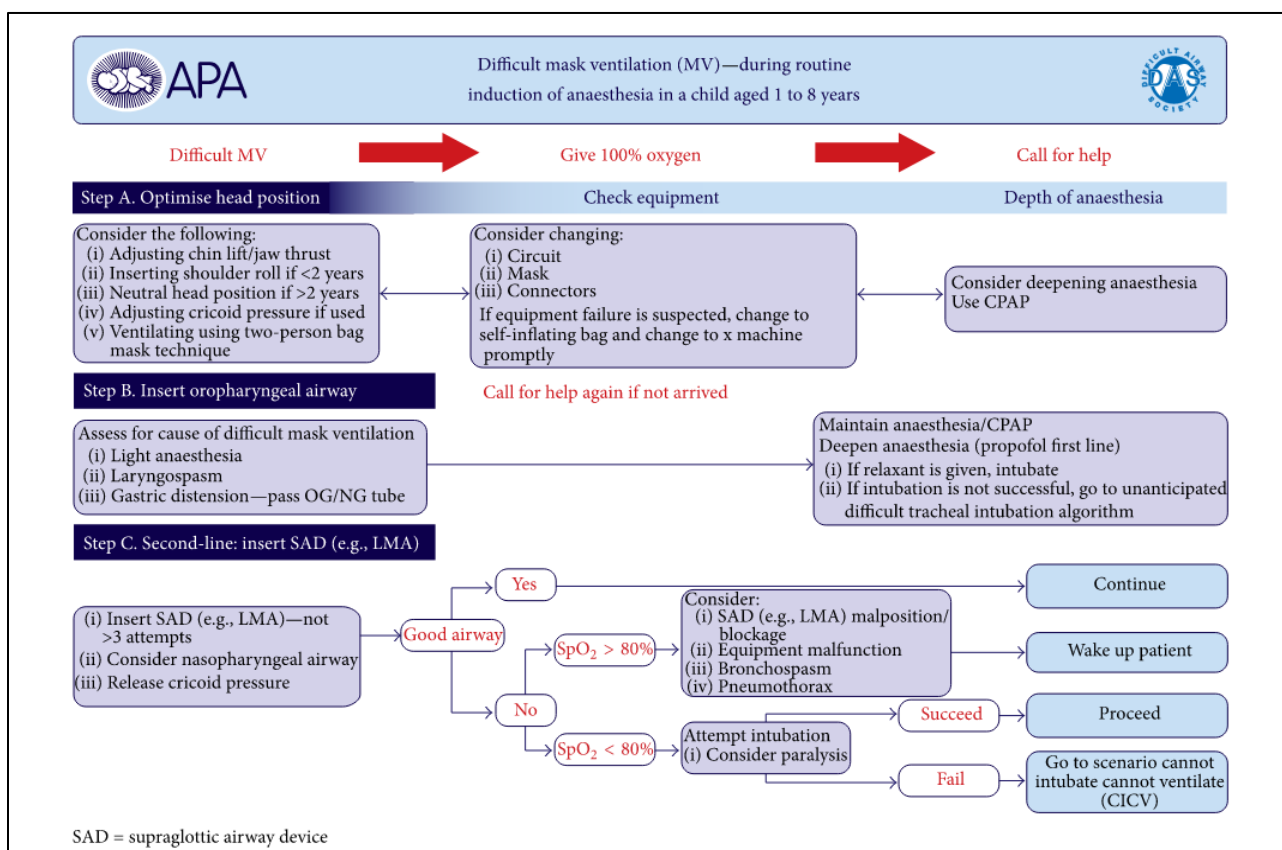
Fig. 1: Guideline for the management of difficult mask ventilation in children aged 1-8 years, published by das (Difficult Airway Society).
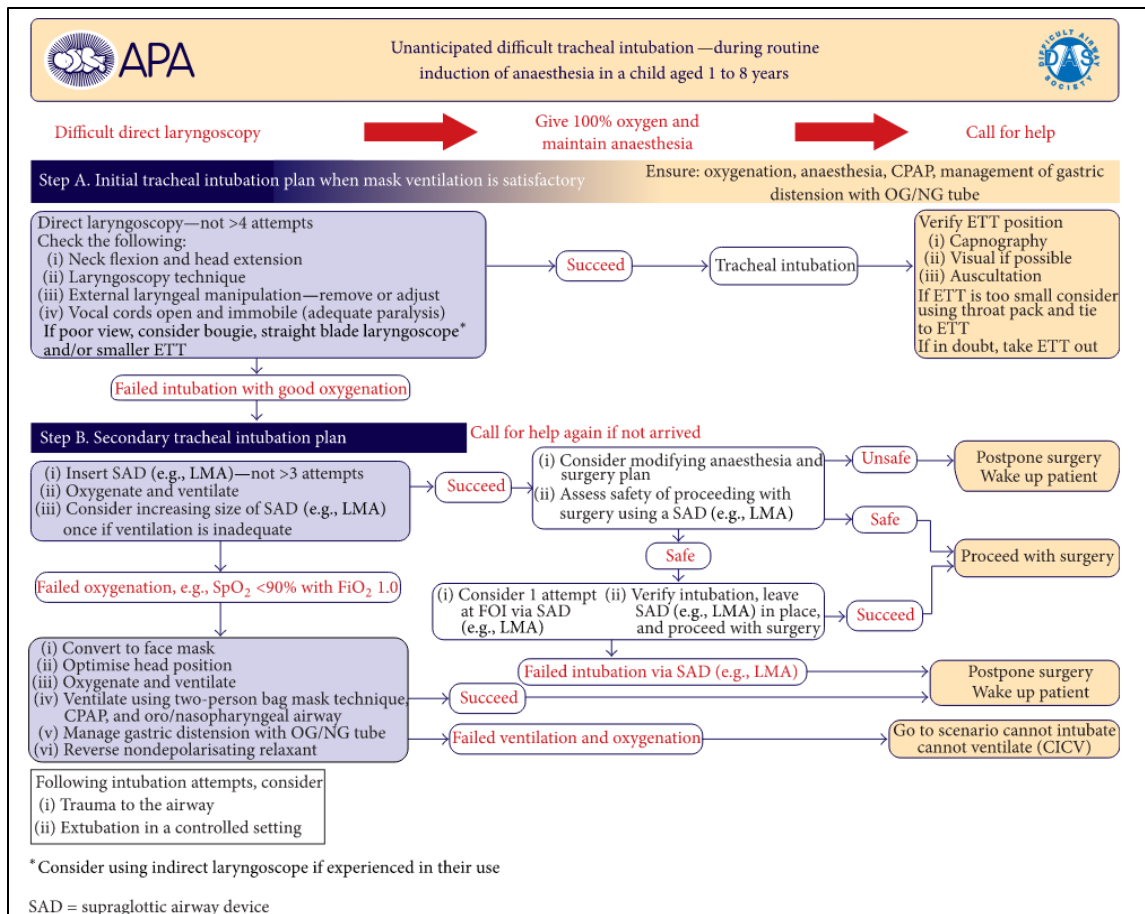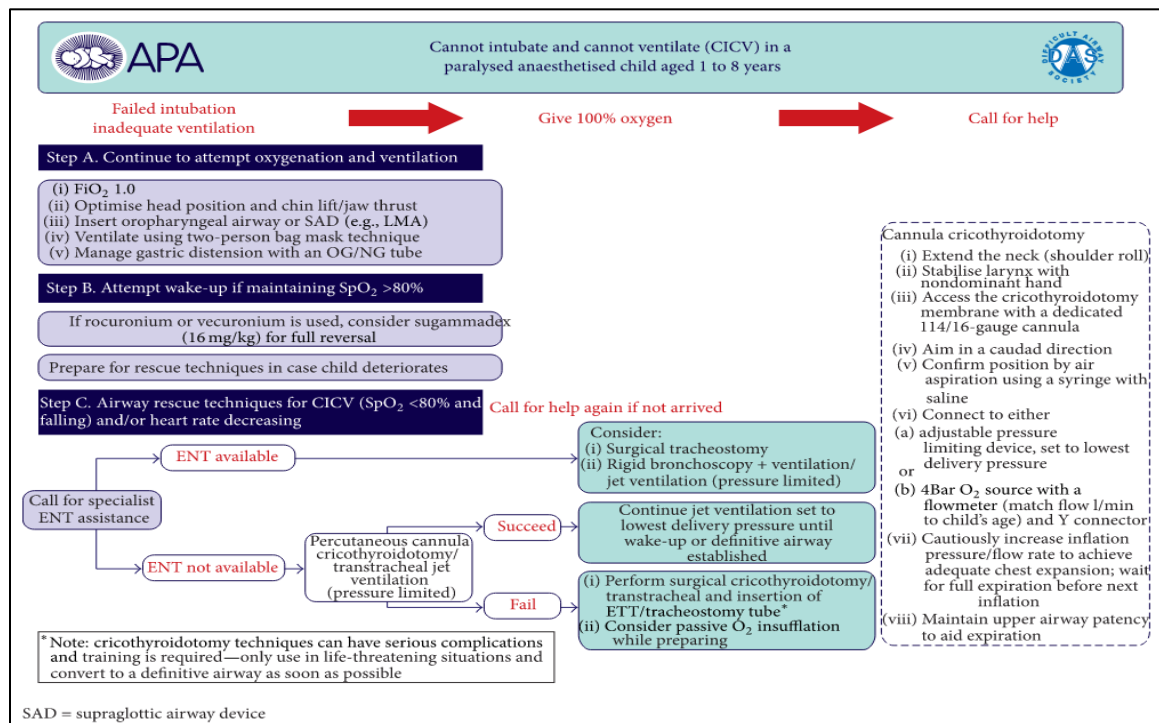
Fig. 2

Fig. 3: Guidelines for the management of CICV scenario in children aged 1-8 years, published by DAS (Difficult Airway Society).

Discussion

Larsen syndrome is differentiated from other related abnormalities like Boomerang dysplasia, diastrophic dysplasia, atelosteogenesis, atelosteogenesis and spondylocarpotarsal synostosis syndrome based on the clinical features and the underlying genetic defect. LRS can present with a wide range of phenotypic variation, even within families. Mutations are in the form of sequence variants, exonic or whole-gene deletion/duplication, the mutation detection frequency is 100%. Inheritance of this form is autosomal dominant. The syndrome is compatible with life when mild and may go unnoticed till adulthood. Prenatal diagnosis is possible as it shows growth deficiency.[4] Following its initial description, there have been multiple reports describing other associated anomalies. An autosomal recessive form of LRS due to carbohydrate sulfotransferase 3 deficiency is also identified. Variations in the severity and phenotypes of Larsen syndrome are described and are associated with 3 different mutations involving LAR1, FLNB and CHST 3. Intra-familial variation autosomal recessive inheritance, have also been suggested. Commonly Larsen cases, have autosomal dominant inheritance, however, recessive forms are also described. And de novo mutations with no family history are described. Most of the patients have de-novo mutations with no family history. Other forms or inheritance due to parental mosaicism is reported. Larsen syndrome is characterized by congenital foot deformities (equinovarus or equinovalgus); dislocations of the hip, knee, elbow and shoulder; short stature; spinal deformities (scoliosis, cervical kyphosis, atlantoaxial instability, vertebral fusion, dysraphism, cervical myelopathy); abnormalities of phalanges (spatulate fingers, pseudoclubbing, supernumerary carpal and tarsal bone ossification centres); cleft lip and palate, hearing loss (malformed ossicles), laryngotracheobronchomalacia, cardiac anomalies, distinctive "dish-like" craniofacies (prominent forehead, hypertelorism, palate deformities, flattenned nasal bridge, malar flattening) and brain abnormalities (microcephaly, agenesis of corpus callosum). Intelligence is normal. Furthermore, Larsen syndrome is characterized by short stature (final adult height less than 152cm), a defective collagen formation causing hyperlaxity and joint dislocations involving hip, knees, elbows, feet have dysplastic epiphyseal centers (equinovarus or equinovalgus) with short metatarsals, supernumerary tarsal bones, delayed coalescence of calcaneal ossification centers. Hands display, cylindric fingers, spatulate thumbs, short metacarpals, supernumerary carpal bones, multiple carpal ossification centers, with short nail.[2]

Spinal deformities, with spinal cord compression, leading to myelopathy, include cervical vertebrae hypoplasia, subluxation or fusion of the cervical vertebrae, dysraphism, cervical kyphosis, scoliosis, wedged vertebrae, spondylolysis, spina bifida occulta. Phalanges are abnormal with spatulate fingers, pseudoclubbing and carpus and tarsus have supernumerary ossification centres.

Other abnormalities include cleft lip and palate, conductive hearing loss (malformed ossicles), cardiac anomalies. Skull show features of flattened frontal bone, small skull base, shallow orbits. Face is characteristic with prominent forehead, anterior corneal lens opacities, hypertelorism, flattened midface, depressed nasal bridge, hypodontia. Intelligence is usually normal, however brain abnormalities (microcephaly, agenesis of corpus callosum) have been described. Cardiac lesion might include the presence of aortic dilatation, atrial septal defect, ventricular septal defect. Respiratory system, external features are pectus excavatum, pectus carinatum. Airways present with tracheal stenosis, laryngotracheobronchomalacia. Genitourinary system, internal genitalia (male)-cryptorchidism.[1-4]

Though there is no fixed criteria for definitive diagnosis, which is made on multifactorial elements, both genetic and clinical. Anaesthetic implications and complications of Larsen Syndrome, stem from the underlying hyperlaxity which characterises the disease. The diagnosis of LRS can be missed or misdiagnosed if the clinician does not maintain a high index of suspicion. Patient often presents in early infancy or childhood for correction of clubfoot, palatal deformities or hernia. A clinical diagnostic criterion was proposed by Rodriguez et al. Though the involvement of the spine was initially thought to be minor, it has subsequently been identified as a major cause of disability in these children. The orthopaedic defects in LRS like club foot and knee dislocation respond poorly to conservative management. This necessitates early operative intervention. Most affected children may need more than one sitting of anaesthesia as defects affect bilateral and multiple joints. A proactive anaesthetic plan is necessary to optimise airway, C-spine and systemic management to prevent secondary tetraparesis. The main objective in airway management is to secure the airway and maintain oxygenation irrespective of patient age. Paediatric airway management is a challenging entity which requires careful assessment, preperation and management, in a safe and scientific manner to ensure prevention of morbidity and potential mortality as well.[7]

There are various ongoing developmental changes, ranging from birth to adulthood, in the skull, oral cavity, larynx and trachea. There are several differences between the paediatric and adult airway, which warrants close consideration, to prevent, the fortunately rare situation of, paediatric cannot intubate cannot ventilate (CICV) scenario, leading to catastrophic consequences.[8] The narrowest part of the airway is at the level of the cricoid cartilage, which is subglottic, however, recent MRI studies, are confirming its at the glottis level, as that of for adults.[9] In infants and young children, the head is large relative to the body with small facial structures because of the absence of the paranasal sinuses.[10] The oral cavity is small with a large tongue.[11] The larynx is more conically shaped, anterior, which can be easily moved by external manipulation. The long, narrow, floppy, U or V-shaped epiglottis, makes it necessary to lift it to improve the glottis view during direct

laryngoscopy. The glottis is higher in relation to the spine in neonates (C2/C3) and descends to its usual position at C5 after 2 years. However, ellipsoid shaped cricoid ring, with a mucosal layer, which is highly susceptible to trauma, which can lead to increase in airway resistance due to oedema.[12]

Physiologically, paediatric patients are more prone for hypoxia and respiratory acidosis. Neonates and children upto the age of 3 years are obligatory nasal breathers, having low functional residual capacity, higher oxygen demand, increased carbon dioxide production, increased closing capacity, leading to rapid desaturation, with no tolerance for aponea. Syndromic children, such as, Pierre Robin Sequence, Goldenhar, Treacher Collins, Apert, have associated cardiac, neurological, metabolic, endocrine anomalies in addition to airway difficulties. Larsen syndrome children, present for correction of orthopaedic deformity and cervical spine stabilization and decompression, generally, have fewer cardiac abnormalities, but airway and spine issues.

Airway assessment is to scrutinize and categorize the degree of difficulty and its management in a safe and scientific manner. This includes proper history, which reveals any previous issues with anaesthetic management, ongoing or resolving respiratory tract infections, warranting the need to postpone elective procedure upto 4-6 weeks, if there are evident symptoms, to reduce the risk of perioperative laryngo/bronchospasm. Thorough clinical examination, with presence of abnormal faces, craniofacial abnormalities, swellings, dentition, adequacy of mouth opening, mallampati score, thyromental distance, neck movement (flexion/extension), as deemed appropriate with patient cooperation. Based on these findings, the airway can be classified as unanticipated or anticipated difficulty, and the management planned accordingly, making it easy and safe. Careful management at a tertiary level centre for challenging cases brings down the morbidity and mortality to near nil to minimum, requiring experience and skill.[13] With the advances in technology, the video laryngoscopy as been introduced, for clearer visualisation of the airway, by its wide and high resolution view of the airway, making it a useful tool in the airway armamentarium. Scientific evidences support the use of video laryngoscopy among paediatric patients.[14]

The difficult airway algorithms as per the respective societies both American Paediatric Association (APA) and DAS (Difficult Airway Society) are explained in the Fig.1-3.[15]

Spinal Anomalies

There were four children with spinal abnormalities. However, none had necessitated primary spinal correction. Even simple manoeuvres like cricoid pressure may worsen intubating conditions or worsen C-spine instability, in the presence of AAD. This demands considerable skill, the presence of an experienced anaesthetist is mandatory. Personnel in the operation theatre, recovery area and inpatient units should be made aware of the nature of the spinal anomalies and utmost care should be taken to ensure gentle handling and correct positioning in all clinical settings. These patients should be considered to have an unstable spine unless proved otherwise.[3]

Hypotonia cervical decompression and fusion, closed reduction, open reduction of hip dislocation, casting, bone shortening, ligament excision are some of the procedures requiring early correction under general anaesthesia.

Minor trauma leading to quadriplegia and death have been reported.[3] These patients should be handled gently and positioned carefully. The association of this syndrome with cervical spine anomalies, frequently, mandates an X-ray of the cervical spine with extension and flexion lateral views. Postoperative croup due to the presence of subglottic stenosis is common and has been reported even when a smaller size endotracheal tube (ETT) is used.[3] Whenever possible a supraglottic airway device should be preferred for securing the airway.[4] This not only minimizes manipulation of the neck but also decreases postoperative coughing and the risk of airway collapse on emergence due to airway malacia.[5] These patients tend to have similar cardiac profile to Marfan's syndrome and therefore a preoperative cardiac evaluation is warranted. Intraoperative cardiac arrest has been reported in a patient with cardiac compromise during spinal surgery.[6] A total intravenous technique with propofol may be a good alternative if general anaesthesia cannot be avoided. Regional analgesia has an important role to play since the surgeries are very painful, and the use of opioids may further contribute to perioperative respiratory problems needing close monitoring.[4] The use of caudal epidurals has not been reported in these children, irrespective of its several well known advantages. This is probably because of the high incidence of vertebral instability, presence of spina bifida and also maybe because majority of the cases reported underwent surgery of the spine. Addition of morphine prolonged the analgesic effects considerably. More recently, an innovative method of relieving airway obstruction in a patient of Larsen syndrome presenting with posterior cervical arthrodesis, where the median mandible was split for an anterior mediastinal tracheostomy, has been described.[17]

Mild and flexible cervical kyphosis is treated by posterior spinal fusion, however, severe kyphotic defects, will require, anterior decompression and circumferential arthrodesis. These patients usually develop myelopathic symptoms. Therefore, at most care is taken, as there is very high risk of spinal cord injury, especially during decompression manoeuvres and stabilization of the reconstructed cervical spine. Preoperative radiological screening for early detection and treatment of cervical kyphosis in mandatory.[16]

We analysed a cohort of children with LRS undergoing orthopaedic intervention and detail the anaesthetic management in these children. Since this is rare disorder no single surgeon or anaesthetist will have sufficient exposure to be able to manage all the manifestation unless working in a centre catering to children with multiple congenital deformities. Each of these has a specific anaesthetic implication which is discussed in the next section.

In our study, we observed, majority of the cases, had orthopaedic corrective deformities, few with airway, spine and cardiac abnormalities. Careful scrutiny, will help plan and manage these cases safely and effectively.

Conclusion

Larsen syndrome is a well-known entity, even amongst the Indian race, which has to be closely looked for and carefully managed in the entire perioperative care for safer outcomes, reduced length of stay in the hospital and improved patient and provider satisfaction.

Limitations

Number of cases during the stipulated period of study were less.

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Conflict of Interest: None.

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