

# Anaesthesia Recommendations for Patients with Loeys-Dietz Syndrome

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## Abstract

Loeys-Dietz Syndrome is a otosomal dominant connective tissue disorder which has characteristic triad with

- a) Arterial tortuosity, aneurysms or dissections;
- b) Hypertelorism; and
- c) Bifid uvula or cleft palate.

This review summarizes the features of anesthesia management in this syndrome

**Keywords:** Loeys-Dietz Syndrome; Anesthesia management

**Abbreviations:** LDS: Loeys-Dietz Syndrome; TGFBR1: Transforming Growth Factor-Receptor Type 1; ARB: Angiotension Receptor Blockers; ACE: Angiotension Converting Enzyme

## Introduction

Loeys-Dietz Syndrome (LDS), is a rare connective tissue disease which is classified under Marfan-like dysfunctions and described by Loeys et al. [1]. LDS is inherited in an otosomal dominant manner. Four types of LDS are described according to mutations in genes which play important roles in cell signalling that promotes production of proteins for tissue growth and development. While the cytokine transforming growth factor-receptor type 1 (TGFBR1) gene mutations cause type I and the TGFBR2 gene mutations cause type II, mutations in the SMAD3 and TGFBR2 genes result in type III and type IV, respectively. The most common forms of disease are types I and II [2]. The prevalence of this syndrome is less than 1/1 000 000 [3]. The diagnostic triad of this syndrome is as follows:

- a) Arterial tortuosity, aneurysms or dissections;
- b) Hypertelorism; and
- c) Bifid uvula or cleft palate.

Although, arterial tortuosity is observed mostly in the head and neck vessels, it can occur other vessels as well. The clinical findings

for musculoskeletal system involvement can be arachnodactyly, joint laxity, pectus deformities, scoliosis, dolichosternomelia, talipes equinovarus, camptodactyly, and cervical spine instability. Cardiovascular findings can be aortic dilatation and dissection, bicuspid aortic valve, and congenital heart disease such as atrial septal defect, patent ductus arteriosus. Central nervous system anomalies such as Chiari malformation and hydrocephalus can be observed. However, the life threatening complications that determine the prognosis are mostly cardiovascular system related findings like aortic root aneurysms, arterial tortuosity, aneurysms of other vessels, patent ductus arteriosus, and atrial septal defect.

## Frequently Performed Surgery Types

Patients can have surgeries (emergency or elective) under anesthesia for cardiovascular (aortic aneurysm repairment, aortic valve replasman), orthopedic (musculoskeletal system anomalie repairment), neurosurgical (for vascular, craniosynostosis, chari malformation and hydrocephalus), ophtalmic (for cataracts, strabismus, amblyopia, and exotropia), and general (for inguinal, umbilical and hiatal hernia repairment, splenic or bowel rupture).

## Type of Anesthesia

Publications about LDS in literature are usually about surgical treatments of anomalies and associated symptoms. Anesthesia for patients with LDS should be special. Anesthetic technique should be decided according to the pathologies that patients have by an experienced anesthesiologist. Aorta and other big vessels as well as all cardiovascular system are affected by hypotension or hypertension during anesthesia because of lack of elasticity in the vessels. Anesthetic approach for Marphan syndrome can be applied for LDS patients since it is described as Marphan-like syndrome.

## Additional Necessary Preoperative Diagnostic Procedures

First, it should be investigated if there are cardiovascular anomalies in children since these anomalies usually asymptomatic in earlier ages. Diagnostic tests such as electrocardiogram, echocardiogram, or cardiac magnetic resonance imaging should be ordered preoperatively to rule out cardiac or aortic pathology. In case of aneurysms, it should be consulted with neurovascular and cardiovascular surgeons for surgical plan. Although, the risk of aortic dissection increases at or above the 5.0cm aortic root dimension in Marphan syndrome, dissections have been reported in patients with LDS types I, II, or III when aortic root dimensions are 3.9, 4.0, 1.3 cm, respectively. Also, dissections have been reported in LDS type IV patients with aortic root dimension under 5.0cm [4-6]. When the maximal aortic root dimension reaches 4.0cm in adult patients with LDS type I or II, surgery is performed, however, in children surgery can be postponed until the aortic root reaches 2.0-2.2cm to accommodate adult-sized graft. Children with mild craniofacial features and slowly progressive aortic root dilatation, surgery can be delayed until aortic root dimension is 4.0cm, however, children with severe craniofacial features, rapidly progressive aortic dilatation (0.5cm over a year), as well as family history of aggressive aortic disease earlier surgery should be considered.

To assess the instability of cervical spine, X-rays at flexion and extension positions should be performed. In the presence of spontaneous pneumothoraces history, chest X-ray also should be ordered. Pulmonary function tests should be done in patients with severe scoliosis to evaluate the extent of restrictive lung disease. Ophthalmic examination and required treatments should be performed. These patients are prone to have high prevalence of immunologic features, so for this reason allergy history should be taken carefully.

## Particular Preparation for Airway Management

Airway management might be hard due to craniofacial deformities, cleft palate, micrognathia, retrognathia, cervical spine abnormalities, subluxations, or instability. Difficulties of anesthesia should be explained to patients and their relatives and consent form asked to be signed. Difficult intubation and airway management table should be ready. During preoperative examination for airway

evaluation, deformities, situation of teeth, as well as opening of nostrils should be recorded. Mallampathy classification, evaluates degree of appearance of palates in adults, can not be used for babies and young children. It can only be used in older children who can apply commands [7]. Intubation using videolaryngoscopy can be preferred in these patients due to difficult airway management and cervical spine instabilities [8]. Anesthesia should be planned according to the area of surgery, duration of surgery, and degree of invasivity. Also, an alternative plan should be thought. Airway masks may not be appropriate and ventilation might be difficult. Airway obstruction might be observed due to structural deformities like cleft palate [9]. Laryngeal masks can be used successfully if general anesthesia is not required intubation and the duration of anesthesia is less than two hours. Hypertensive response to intubation and risk of aortic dissection would be eliminated using laryngeal masks. If endotracheal intubation will be applied, to prevent hemodynamic changes due to intubation precautions should be prepared. In the presence of pneumothoraces and restrictive lung disease, lung protective strategies should be applied and use of N<sub>2</sub>O should be avoided.

## Preparations for Transfusion or Administration of Blood Products

There is no evidence that shows that LDS patients with pre-existing coagulation abnormalities have a higher risk of blood transfusion.

## Preparations for Anticoagulant Treatment

There is no information suggesting anticoagulant treatment except for patients who underwent valve or aortic root replacement surgery. Patients required anticoagulation due to prosthetic valve should be offered a bridging therapy prior to elective surgery. Bridging therapy is not offered to patients newly started oral anticoagulant treatment for atrial fibrillation because of its quick and short duration of effect [10,11].

## Precautions for positioning, transportation, and/or mobilization

To prevent joint injury and dislocations due to musculoskeletal system deformities, patients should be positioned appropriately and areas stay under pressure should be supported using soft position pillows. Especially in prone position, head should be held in neutral position and excessive rotations should be avoided because of possible cervical spine instability.

## Possible Interactions between Anesthetic Agents and Patients' Long Term Medications

Anti-hypertensive medications (angiotension receptor blockers (ARB),  $\beta$ -blockers, and angiotension-converting enzyme (ACE) inhibitors):  $\beta$ -blockers should be continued perioperatively. Side effects of perioperative  $\beta$ -blockage are bradycardia and hypotension. To continue ACE inhibitors and ARBs until surgery

may increase the risk of perioperative hypotension, however, it should be kept in mind that cease of ACE inhibitors prior to surgery may lead postoperative hypertension [12].

## Anesthesia

Anesthesia induction requires a special care in these patients. Severe hypotension or hypertension should be avoided. There is not any described method for choosing anesthetic agent [13]. Anesthesia induction via intravenous route can cause hypoxia following sudden lost of airway management and apnea in patients with difficult airway. However, anesthesia induction via inhalation gives a chance to control airway and continue of spontaneous breathing. Emergency cardiac medications should be ready to treat radically in case of development of critical situations like hypotension and/or rhythm problems. As a vasopressor phenylephrine should be preferred over ephedrine that may induce tachycardia through its beta-adrenergic effect. Central lines should be placed using ultrasound because of cervicovertebral arterial tortuosity by an experienced anesthetic team.

Antibiotic prophylaxis for high risk procedures should be thought in patients who have prosthetic valve or have prosthetic material for valve repairment; had endocarditis previously; or have congenital heart disease [14]. High risk procedures that suggested endocarditis prophylaxis are follows: dental procedures (only gingival or periapical region manipulations, oral mucosa perforations), airway procedures (in case of infection, during bronchoscopy, laryngoscopy, transnasal, or endotracheal intubation), gastrointestinal and urogenital procedures (in existence of infection, gastroscopy, colonoscopy, cystoscopy, and transeusophageal echocardiography), skin and soft tissue procedures (if there is no infection, no need any antibiotic prophylaxis) [15].

## Monitoring

Additional to routine anesthetic monitoring (ECG, non-invasive blood pressure, SpO<sub>2</sub>, end-tidal CO<sub>2</sub>) airway pressures, anesthetic gases, core temperature, and neuromuscular blockage should be monitored. Invasive-blood pressure monitoring should be used intraoperatively to notice sudden changes.

## Possible Complications

Complications of LDS are secondary to conditions, symptoms, or diseases that are involved in LDS. There are rupture of aortic aneurysm, cerebral hemorrhage, cardiac arrhythmias, rupture of spleen or bowel, pneumothoraces, aortic dissections during pregnancy or immediate postpartum, and rupture of uterine.

## Postoperative Care

Postoperative monitoring should be decided according to type of surgical procedure, problems developed intraoperatively, ventricular function, as well as condition of aortic root. An intense follow up might be needed for obstructive sleep apnea syndrome in children with craniofacial abnormalities. These patients can be

monitored postoperatively in a first step intensive care unit. Kuisle et al. [16] reported an adolescent patient with LDS and undiagnosed adrenoleukodystrophy who developed adrenal crisis. To prevent excessive endogenous catecholamine production, it is essential to control pain and anxiety in these patients.

## Ambulatory Anesthesia

There are no reported experiences of patients with LDS in the ambulatory setting.

## Obstetrical Anesthesia

Although women with LDS tolerated pregnancy well, vaginal delivery, or cesarian section with close follow up and early action was still required, and were accepted as high risk patients. Early delivery and avoiding of intra- abdominal pressure increase while applying cesarian section may decrease obstetric complications risk. As of today, there has been three pregnant LDS patients reported. The first case was a 16 weeks pregnant LDS patient who had successful surgical aortic valve and arch replacement for type A aortic dissection. She had an uneventful cesarian delivery [17]. The second case was an LDS patient who underwent cesarian section without any complications at 34 weeks pregnancy. There was no information about anesthesia for these patients. The third case was an LDS patient 36 weeks pregnant with 3.45cm aortic root dilatation who underwent c- section under general anesthesia without any complications [18].

LDS was described as Morphan-like syndrome in 2005 and anesthesia management can be adopted from anesthesia application for patients with Morphan syndrome until described. Higher complication risks including death from aortic dissection was reported in pregnant women with aortic dimension over 4.5cm in Morphan syndrome [19]. Since LDS is more severe, higher risk of vascular complications can be expected. In female patients who have around 4.0cm aortic root, aortic root replacement should be considered before pregnancy. Whole aorta should be evaluated before pregnancy. If needed, surgical aortic root dilatation can be applied before 28 weeks of pregnancy [20].

## Management of Neuraxial Analgesia or Anesthesia

Neuraxial anesthesia might bring some technical difficulties due to scoliosis. Also, dural ectasia which is widening or ballooning of the dural sac around the spinal cord might be encountered in these patients. Dural estesia develops due to structural changes of elastin. This might lead to dural puncture during epidural catheter placement or unsuccessful spinal anesthesia [21,22]. For this reason, ultrasonographic evaluation of lumbar spinal area is suggested before neuroanesthesia [23]. Continue spino- epidural anesthesia can be preferred in these patients. This gives an opportunity to complete to the cesarian section by epidural anesthesia after an unsuccessful spinal anesthesia as well as to achieve post- operative pain management.

### Management of General Anesthesia

Hemodynamic responses to laryngoscopy and surgery are important for LDS patients with dilatated aortic root during general anesthesia. Hemodynamic responses to laryngoscopy and surgery can be prevented by continuing beta- blocker treatment and by administering an iv opioid during the induction of anesthesia. Ultra- short acting remifentanyl which has no important effects in newborns can be preferred. Remifentanyl 0.5-1mcg/kg bolus administration effectively reduces hemodynamic and catecholamine release responses in pre eclampsia, but still it should be kept in mind that it can cause temporary respiratory depression in newborns [24,25].

There is no evidence that one anesthetic technique is superior to another one [22]. It is more essential to avoid hypertension rather than mild hypotension. For this reason, one might said that, this problem can be attenuated using neuraxial anesthesia instead of general anesthesia. To determine sudden arterial pressure changes in pregnant LDS patients, invasive arterial pressure monitoring is required. Even, transesophageal echocardiogram can be suggested. Also, postoperative pain management should be planned. It is suggested that these patients should be cared in intensive care unit for postoperative 24hrs for possible aortic arterial or hollow organ ruptures.

**Table 1:** Anesthetic preparations for patients with LDS.

Preoperative evaluation	a) Cervical spine X-rays in flexion and extension position performed at diagnosis to assess for instability
	b) Full vascular imaging prior to pursuing pregnancy
	c) Consultation with cardiovascular/neurovascular specialists for surveillance and/or surgical plan with presence of aneurysms
	d) Pulmonary consultation or sleep study for sleep apnea in presence of clinical symptoms
	e) History of allegry should be carefully taken. Children with frequent surgical procedures may have developed Latex allergy.
	f) Check for airway difficulties
	g) Inform the patients or relatives about relevant issues of the underlying disorder with regard to planned anesthesia. Discuss specific anesthetic risk of general or neuroaxial anesthesia.
	h) If needed, endocarditis prophylaxis should be administered.
	i) If needed, deep vein thrombosis prophylaxis should be administered.
	j) Beta- Blocker treatment should be continued. Patients treated with ACE- I and ARBs should be carefully observed for hypotension.
Anesthesia considerations	a) Airway management table and alternative plans should be prepared for patients expected to have difficult airways.
	b) Invasive arterial pressure monitoring should be applied.
	c) A smooth anesthesia induction should be performed by avoiding hypo- hypertension.
	d) Avoid peroperative hypertension and apply careful hemodynamic monitoring during surgery.
	e) During central catheterization, use ultrasonography.
	f) During neuraxial anesthesia, use ultrasonography to assess possible dural ectesia
	g) During positioning, areas under pressure should be supported using position pillows.
	h) During extubation, avoid hypertension.
Postoperative Care	a) Postoperative acute pain management should be planned.
	b) Prevent hypertensive attacks.
	c) 24 hour intensive care unit monitorization.

### Conclusion

Although LDS is a rare disease, it should be considered in terms of anesthesia as it may require early and repeated surgical intervention; also has many medical features that threaten life.

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