POSSIBLE ROLE OF CAUDAL EPIDURAL ANESTHESIA IN EMERGENCE AGITATION AMONG PEDIATRIC POPULATION

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Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Background: Shivering can be caused by neuraxial as well as general anaesthetics. Because of the heterogeneity of the studies, estimating the incidence of shivering secondary to neuraxial block is tricky, however it is estimated to be around 55%. Spinal anaesthesia lowers core body temperature faster than epidural anaesthesia in the first 30 minutes following the block. Both strategies cause the temperature to drop at the same rate after 30 minutes. the recovery unit. Shivering not only causes psychological stress in the patient, but it also causes physiological changes such as increased oxygen consumption by 200–600%, increased carbon dioxide production, increased blood pressure, increased risk of myocardial ischaemia, infection, and bleeding, and increased minute ventilation. It also causes hypoxaemia, lactic acidosis, increased intraocular pressure, and intracranial pressure, as well as impeding patient monitoring tools like the electrocardiogram (ECG), non-invasive blood pressure (NIBP), and peripheral oxygen saturation (SpO2). Temperature monitoring is required for patients receiving anaesthesia, but due to the unavailability of an accurate non-invasive core temperature monitor, core temperature is frequently under-monitored during spinal anaesthesia, and significant hypothermia often goes unnoticed in these patients. For monitoring core temperature, disposable thermocouple and thermistor probes are utilized. They are a reasonably accurate (±0.5°C), low-cost, and dependable method. Infrared monitors detect the heat emitted by radiation and can measure the temperature of the tympanic membrane and forehead skin, however they are less accurate. Dexmedetomidine is effective and comparably better than ketamine in preventing shivering after spinal anesthesia. Dexmedetomidine also provides sedation without respiratory depression and favorable surgical conditions. However, with its use a fall in blood pressure and heart rate is anticipated.

Keywords: hypothermia, Shivering, anaesthesia

DOI: - 10.53555/ecb/2023.12.Si12.287

Introduction

Eckenhoff et al. were the first to document a phenomenon known as emergence agitation (EA), which involves children displaying signs of distress, confusion, and restlessness upon awakening from anesthesia. This was observed in children who had undergone procedures like tonsillectomy, thyroidectomy, and circumcision, while being anesthetized with substances such as ether, cyclopropane, or ketamine **(1).**

In the present day, approximately 4 million children worldwide undergo anesthesia annually and EA has been recognized as a notable issue during the recovery phase. The reported incidence of EA varies widely, ranging from 10% to 80 % **(2).**

- **Definition:**

Emergence agitation (EA) is a dissociated state of consciousness characterized by irritability, crying, shouting, screaming, non-purposeful restlessness and disorientation **(2).**

The terms "emergence agitation," "emergence delirium (ED)," and "excitement" have been used interchangeably to describe a child who displays irritability, uncooperativeness, and inconsolability upon awakening from anesthesia. However, there are differences in the definitions and clinical presentations of agitation and delirium **(1).**

Agitation refers to excessive motor activity, which is commonly observed in both children and adults during the postoperative period. On the other hand, delirium is more challenging to diagnose, prevent, or treat, and it has distinct clinical features. Delirium is characterized by an acute state of confusion accompanied by cognitive impairment, including perceptual disturbances and hallucinations. It is similar to anxiety in terms of mood alteration but differs in the presence of cognitive deficit **(3).**

Unfortunately, differentiating cognitive impairment in children is challenging, making it difficult to make accurate diagnoses and prescribe appropriate therapy for emergence agitation. Consequently, the terms emergence agitation and emergence delirium are used interchangeably **(2).**

- **Etiology:**

Numerous studies have been conducted to investigate the underlying causes of emergence agitation (EA), which is a non-specific symptom that can result from various sources of internal discomfort, including pain and anxiety.

1. Physiological Compromises:

Metabolic disturbances, hypoxemia or bladder distension can contribute to post-anesthetic problematic behaviors in children. These physiological factors can cause discomfort and agitation during the emergence from anesthesia **(4)** .

2. Pain and Anxiety:

Inadequate pain management or high levels of anxiety can lead to agitation in children. Proper management of pain through analgesics and addressing anxiety with reassurance and benzodiazepines (BZD) can help alleviate agitation **(4) .**

3. Surgical and Patient-Related Factors:

Certain factors related to the surgery and the patient can influence the occurrence of EA. Factors such as the invasiveness of the procedure, duration of surgery, and individual patient characteristics can contribute to post-anesthetic behaviors **(5).**

4. Anesthesia-Related Factors:

Anesthesia techniques and medications used can impact the likelihood of EA. Rapid emergence from anesthesia and the specific type of anesthetic employed can influence the occurrence of agitation **(6)**.

5. Preexisting Psychosocial Pathology:

Children with preexisting psychological or behavioral conditions may be more susceptible to EA. These conditions could include anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), or autism spectrum disorders **(7).**

6. Physiological Abnormalities:

Children with underlying physiological abnormalities, such as cardiovascular or respiratory conditions, may be at a higher risk of experiencing agitation during emergence from anesthesia **(7).**

7. Environmental Factors:

The environment in which the child awakens from anesthesia can also play a role. Factors like a hostile or unfamiliar setting may contribute to increased agitation **(1).**

8. Preoperative Anxiety:

Anxiety experienced by the child before the surgery can contribute to post-anesthetic problematic behaviors. Addressing preoperative anxiety through appropriate measures, such as preoperative education and parental presence, can help reduce agitation **(5).**

9. Use of Inhalational Agents:

The specific inhalational agents used during anesthesia can influence the occurrence of EA. Some studies have suggested a higher incidence of agitation with certain inhalational agents **(8).**

It's important to note that the etiology of EA and post-anesthetic problematic behaviors can be multifactorial, and individual children may have varying contributing factors. Understanding these factors allows healthcare providers to tailor interventions and management strategies to minimize agitation and promote a smoother recovery from anesthesia .

- **Incidence of EA :**

The reported incidence of emergence delirium (ED) in pediatric populations can vary widely, ranging from 2% to 80%. The incidence rates are influenced by factors such as the age group being studied, the specific population, and the criteria used to define and assess EA **(9)**.

- **Susceptibles:**

Certain populations are more susceptible to experiencing emergence agitation (EA). Here are some points regarding the susceptibility of different age groups and individuals with specific conditions:

1. Age:

Children between the ages of 2 to 5 years old are more likely to exhibit signs of EA. The incidence of EA tends to decline after reaching 62 months of age. This age range aligns with the developmental stages defined by the American Academy of Pediatrics, which include early childhood (15 months to 4 years old), middle childhood (5 to 10 years old), and early adolescence (11 to 12 years old) **(10)**.

2. Developmental Level:

Individual variations in developmental level within an age group can influence the occurrence of EA. Children who may be experiencing delays or differences in their developmental milestones may be more susceptible to agitation upon emergence from anesthesia **(2).**

3. Mental Disease and Neurologic Conditions:

Children with existing mental diseases or neurologic conditions may have a higher risk of developing EA. These conditions can include psychiatric disorders, neurodevelopmental disorders (such as autism spectrum disorders), or neurological conditions affecting cognitive or behavioral functions. **(11).**

- **Predisposition and risk factors of EA in children:**

A) Age-related factors:

Several studies have highlighted age-related factors in the incidence of emergence agitation (EA) in children, particularly in the preschool age group.

1. Incidence in Preschool Age:

Research has consistently shown a higher incidence of EA in preschool-age children, specifically in the range of 2 to 4 years old. This age group has received significant research attention due to the increased incidence of agitation following anesthesia with sevoflurane compared to school-age children **(3).**

2. Emotional Liability and Stressful Environment:

Preschool-age children often exhibit enhanced emotional liability, which means they can be more susceptible to emotional swings and reactivity. When confronted with a stressful situation in an unfamiliar environment, such as the post-anesthetic recovery area, their emotional response may be heightened, leading to a greater likelihood of agitation **(7).**

3. Immature Hippocampus:

The physiological condition of the hippocampus, a brain region involved in memory and emotion regulation, is still immature in preschool-age children. This immaturity may contribute to their increased vulnerability to agitation in response to a stressful situation like emergence from anesthesia **(3).**

B) Psychological, social and environmental factors related to the operation:

Several psychological, social, and environmental factors have been identified as related to the occurrence of emergence agitation (EA) in children recovering from anesthesia. Younger children, those with impulsive

and emotional behavior, and those who are less sociable and whose parents are more anxious are more prone to developing EA**(2).**

Children who exhibit frequent tantrums and those who suffer traumatic separation from their parents on the way to the operating room tend to exhibit postoperative agitation more frequently, but without exhibiting long-term psychological consequences **(7)**.

C) Premedication:

Premedication is a practice in anesthesia where medications are administered before surgery to help alleviate anxiety, provide sedation, and reduce postoperative complications such as emergence agitation (EA) **(12).**

The association between the uses of midazolam as a premedication in children with EA has been a topic of controversy. Some studies have shown that midazolam can decrease agitation postoperatively following sevoflurane anesthesia. However, other studies have shown no effect or even an increase in agitation with midazolam. It has been suggested that midazolam may decrease agitation by its residual sedative effect at the end of surgery for short procedures or by decreasing preoperative anxiety **(2).**

Other premedication drugs have been used and compared to midazolam. For example, oral clonidine given prior to sevoflurane anesthesia induction in preschool children has been associated with a significant reduction in EA compared to midazolam **(12).**

It is important to note that premedication or preparation programs can modify the preoperative anxiety of the child and the parent, but they cannot modify the child's natural psychological state, including emotionality, activity, sociability, and impulsivity **(12).**

Overall, the use of premedication in children and its association with EA is a complex topic with varying results. Further research is needed to fully understand the effects of different premedication on EA and to develop strategies for effectively managing postoperative agitation in pediatric patients.

D) Postoperative pain:

Postoperative pain is a confounding factor when analyzing trigger factors for emergence agitation (EA) **(13).** The behavioral manifestations of postoperative pain may confound an EA diagnosis. However, it does not appear to be an independent etiologic factor, since even patients free from pain can exhibit agitation, making it a clinical phenomenon that remains irrespective of postoperative pain **(13).**

A higher level of postoperative pain has been identified as a precipitating factor for hyperactive emergence delirium (ED), which is a state of agitation and hyperactivity occurring when a patient wakes from anesthesia **(14).**

E) Type of surgery:

Otorhinolaryngological surgical procedures, such as tonsillectomy, thyroidectomy, and ophthalmological operations, have been associated with an increased incidence of agitation **(1).**

Other types of surgeries that have been associated with an increased risk of emergence agitation in pediatric patients include craniofacial surgery, cardiac surgery, orthopedic surgery,musculoskeletal surgery and abdominal Surgeries**(15)**

F) Inhaled and intravenous anesthetics:

The incidence of emergence agitation (EA) has been studied in relation to different inhaled and intravenous anesthetics. While sevoflurane is often associated with a high incidence of EA, it is not the only inhalational anesthetic implicated in agitation. Desflurane and isoflurane have also been shown to have a comparable incidence of EA, ranging between 50% and 80% **(16) .**

Propofol is an intravenous anesthetic, has been associated with a lower incidence of EA compared to sevoflurane **(16) .**

- **Diagnosis of emergence agitation:**

Assessment tools for emergence agitation include the Pediatric Anesthesia Emergence Delirium Scale (PAEDS), the Pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU) and the Richmond Agitation-Sedation Scale (RASS).These tools assess for behaviors consistent with EA, including

restlessness, inconsolability, and awareness of surroundings. However, these tools cannot differentiate between pain and emergence agitation, which can make it challenging to determine the appropriate treatment **(1).**

To differentiate EA from postoperative pain, the FLACC behavioral scale has been used. The FLACC scale assesses five categories: Face, Legs, Activity, Cry, and Consolability. Each category is scored from 0 to 2, resulting in a total score between 0 and 10. The interpretation of the FLACC scale results is as follows: 0 = relaxed and comfortable, 1-3 = mild discomfort, 4-6 = moderate pain, 7-10 = severe pain or discomfort **(17)**.

Several studies have used Aono's four-point scale to assess the incidence and severity of EA in pediatric patients after anesthesia. The scale has been found to be a reliable tool for diagnosing and quantifying EA.

The incidence and severity of emergence agitation (EA) can be evaluated using Aono's four-point scale, Aono's four-point scale consists of the following categories: 1 = Calm; 2 = Not calm, but could be easily calmed; 3 = moderately agitated or restless; 4 = Exited, disorient. Scores of one and two will be defined as the absence of EA, while scores of three and four will be defined as the presence of EA **(18).**

- **Complications:**

Emergence agitation in pediatric patients can lead to several complications. These complications include increased bleeding from the surgical site, damage to surgical repair, pulling out a surgical drain or an intravenous access and increased pain at the operative site. This phenomenon may also result in physical harm to the child or caregiver and may require additional treatment **(19).**

EA can also be disruptive to the Post Anesthesia Care Unit (PACU), often requiring constant nursing supervision. This can strain nursing manpower resources and increase the chances of parental dissatisfaction about the quality of the child's recovery. Patients with EA are difficult to control, and discharge from the recovery area may be delayed **(19).**

The sacrum bone is roughly like the shape of an equilateral triangle, with its base identified by palpating the two posterior superior iliac processes and a caudal summit corresponding to the sacral hiatus. The sacrum is concaved anteriorly. The dorsal part of the sacrum bone consists of a median crest, corresponding to the fusion of sacral spinous processes. Moving more laterally, intermediate and lateral crests correspond respectively to the fusion of articular and transverse processes. The sacral hiatus is located at the caudal end of the median crest and is created by failure of the S5 lamina to fuse. Sacral hiatus is like the shape of an inverted U, and is covered by the sacro-coccygeal ligament, which is in continuity with the ligamentum flavum. It is large and easy to locate until 7-8 years of age. Later, progressive ossification of the sacrum (until 30 years old) and closing of the sacro-coccygeal angle make its identification more difficult. Note that anatomical anomalies of the sacral canal roof are observed in 5% of patients and this can lead to unplanned dural puncture and subsequent intracranial extension **(20).**

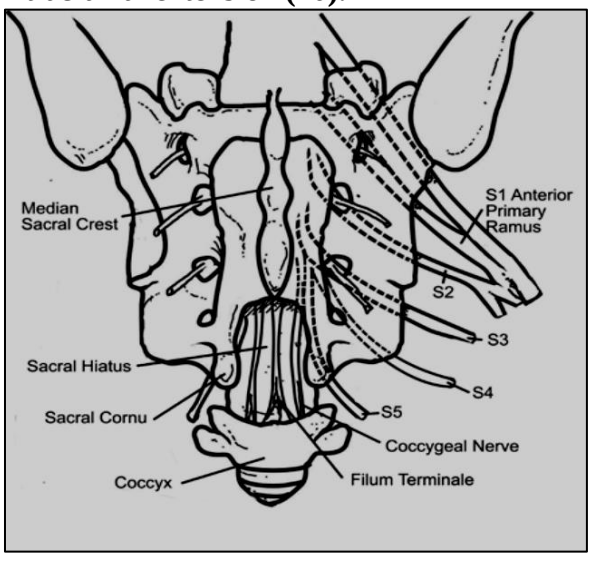

Figure (1): The posterior aspect of the sacrum and sacral hiatus. **(20).**

The sacral canal

The sacral canal is in continuity with the lumbar epidural space. It contains the nerve roots of the cauda equine which leave it through anterior sacral foramina. During caudal block, leakage of local anesthetic agent (LA) through these foramina explains the high quality of analgesia, attributable to diffusion of LA along the nerve roots.

The contents of sacral canal are similar to those of lumbar epidural space, predominantly fat and epidural veins. In children, epidural fatty tissue is looser and more fluid than in adults, favoring LA diffusion **(20).**

The dural sac (i.e. the subarachnoid space) ends at the level of S3 in infants and at S2 in adults and children. It is possible to puncture the dural sac accidentally during caudal block, leading to high spinal anesthesia. Therefore the needle or cannula must be cautiously advanced into the sacral canal, after crossing the sacro-coccygeal ligament. The distance between the sacral hiatus and dural sac is approximately 10 mm. in neonates. It increases progressively with age (>30mm at 18 years), but there is significant inter-individual variability in children **(21) .**

- **Technique of caudal anesthesia**

Caudal epidural anesthesia is a safe and simple technique that is relatively easy to perform as long as the correct landmarks are identified. It is one of the most popular techniques used in children and is usually performed under general anesthesia. The important landmarks for caudal epidural anesthesia include the coccyx and sacral hiatus, which is located between both sacral cornua **(22)**

Caudal epidural anesthesia is a technique that involves placing a needle through the sacral hiatus to deliver medications into the epidural space, Therefore, it is important to use the ideal needle, which should be short-beveled 20 gauge with a stylet, Most authors do not recommend the use of non-specific needle in the sacral epidural approach as advancing of dermal or sub-dermal tissues into the epidural space can cause the formation of a dermoid cyst **(23).**

The advance in ultrasound technique has greatly improved the visualization of spinal sono-anatomy, making it a valuable tool for various procedures, including central neuraxial blockade and spinal anesthesia **(24).**

When performing ultrasound imaging of the lumbar spine, specific landmarks and structures can be identified, including the sacral hiatus, to visualize the sacral hiatus using ultrasound, the ultrasound probe is placed transversely over the coccyx, and scanning is performed in the cranial direction. The bilateral cornua reveal a "frog-eye sign," and the hyperechoic "hump" (sacrococcygeal ligament) becomes visible .The anechoic space between the "hump" and the hyperechoic dorsum of the pelvic surface of the sacrum corresponds to the sacral hiatus

This technique allows for real-time visualization of the sacral hiatus and can aid in accurately guiding needle placement during procedures such as caudal epidural anesthesia **(25)**.

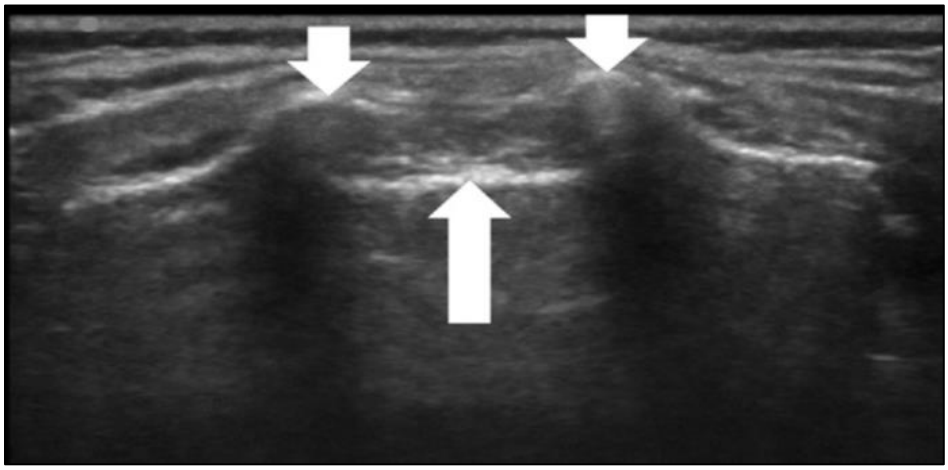

Figure (2): Sono-anatomy of caudal space (frog eye sign): A transverse ultrasound view illustrating the sacrococcygeal ligament (upward arrow) and the two sacral cornua (two downward arrows) **(25)**.

Indications and contraindications:

Caudal anesthesia is commonly used for surgical and post-operative analgesia in the body areas below the infra-umbilical region. It is particularly indicated for procedures such as inguinal hernia repair, cystoscopy/transurethral manipulation, circumcision, anal atresia, treatment of limb ischemia, treatment of intussusception, or cast application for newborns with hip dysplasia, however, the success rate of caudal anesthesia for mid-abdominal surgical interventions, such as umbilical hernia repair is limited and unpredictable **(22)**

Several reasons for this shortcoming:

1- Age-dependent differences:

The levels of sensory analgesia achievable by caudal blockade may vary with age. Studies suggest that the segmental spread of analgesia following caudal administration is more predictable in children up to about 12 years of age **(22)**

In adults, the success rate of caudal epidural block is generally lower, even in experienced hands **(23).**

2- Unpredictable secondary spread:

The spread of local anesthetics in the caudal space can be unpredictable, leading to variations in the extent of analgesia achieved **(22)**

- **Contraindications**

Contraindications to caudal anesthesia in children would include local site infection, coagulopathies, pilonidal cyst, or spinal dysraphism such as tethered cord syndrome. In the presence of other spinal/meningeal anomalies, we suggest conducting a preoperative anatomical investigation by ultrasound or MRI. Performing a careful risk-benefit analysis on this basis can help to identify patients at low risk of inadvertent nerve lesions, who might benefit from regional instead of general anesthesia despite their anomaly (e.g. children with a difficult airway or preterm infants with a history of respiratory depression episodes **(22)**

- **Preoperative assessment:**

During preoperative visit, detailed history patient's age, weight, and baseline vital parameters should be recorded. General physical examinations and examination of the back for any spinal anomalies should be done also.

Routine laboratory investigations such as hemoglobin, bleeding time, and clotting time should be carried out for all patients to rule out any congenital coagulation disorders or therapeutic anticoagulation. Preoperative coagulation laboratory testing is highly indicated if the patient or any of his or her family members have a positive bleeding history.

All patients must be kept fasting as (2 hours for clear liquid and 6 h for semisolid and solid) **(26)**.

- **Patient position:**

The child should be placed in the lateral decubitus position, preferably the left lateral decubitus position, with legs at 90° over the hips and 45° over the knees. The head positioning should observe preservation of free airways **(22)**

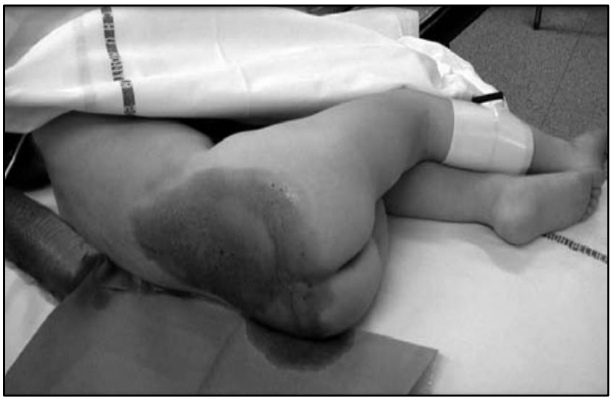

Figure (3): Patient position during caudal anesthesia **(22)**

The sacral hiatus can be identified as the lower vertex of an equilateral triangle having its base in the posterior superior iliac spines **(5).**

Due to the proximity of the anus, skin antisepsis should be carefully done **(5).**

- **Needle insertion technique:**

The needle is inserted 1-2 mm caudally half-way between both cornua, proximal to the vertex of the hiatus, at a 45° angle in relation to the skin. After the loss of resistance characteristic of passing the sacrococcygeal membrane, the needle is repositioned, decreasing the angle to 20°- 30° and it is inserted 2-3 mm into the vertebral canal. Once inside the epidural space, one needs to be careful to avoid advancing the needle any further, since the dural sac in small children can extend to the level of S3-S4 (contrary to adults in which it extends to S2) leading to unintentional dural puncture **(27).**

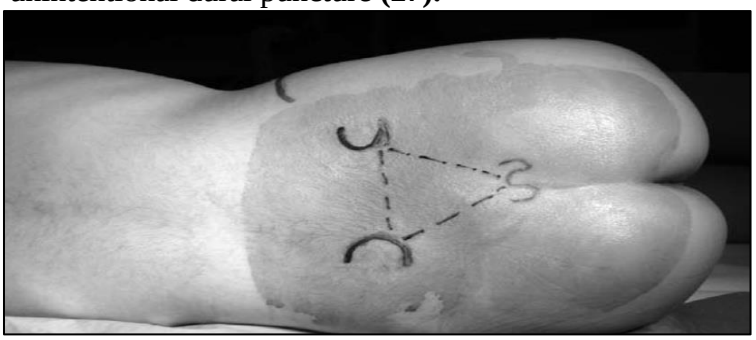

Figure (4): Anatomical land mark of the caudal space. **(28)**

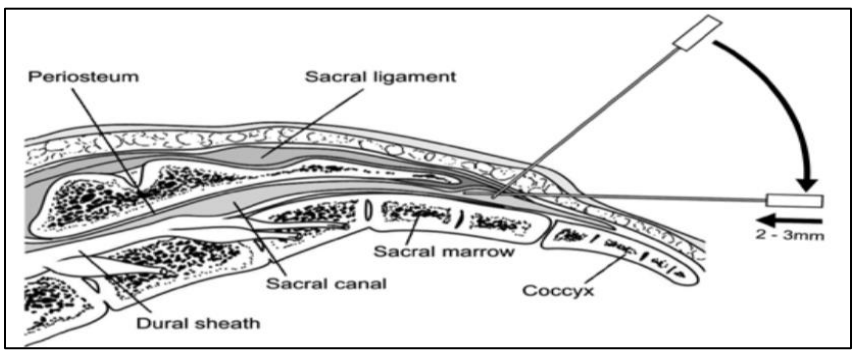

Figure (5): Direction of the needle during caudal block **(27).**

Intravascular or subarachnoid injection should be ruled out by gently aspirating the syringe or maintaining the needle open for 10-15 seconds. However, negative aspiration of blood or cerebrospinal fluid in children is not reliable due to the high complacency of epidural veins and subarachnoid space, which are easily collapsible. Therefore, a test dose of the anesthetic is injected, and after 30-60 seconds, the anesthetic solution is injected slowly with frequent aspirations observing monitoring parameters **(27).**The test dose of a local anesthetic solution with adrenaline 1:200,000 should be given to children, even though its effectiveness is debated. Elevated T-waves or an increase in heart rate can indicate intravascular injection of adrenaline. Systolic blood pressure may rise, but T-wave changes are a more reliable indicator **(29).**

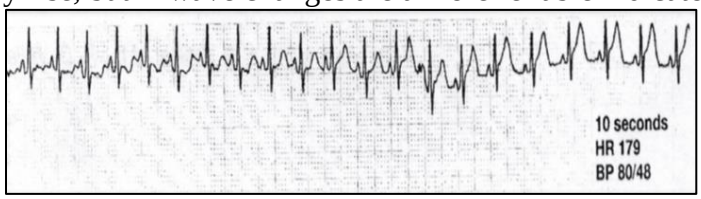

Figure (6): T wave changes during accidental intravascular injection of the test dose **(16) .**

Perforation of the dura mater is rare when the technique is performed correctly.There have been no reports of infectious complications like abscesses or meningitis after single-injection epidural anesthesia. Infections are usually associated with catheter placement for postoperative pain relief. Complications such as neurologic damage, epidural hematoma, infection, and dural puncture are rare when the technique is properly executed **(27).**

- **Volume of local anesthetics according to the required level of anesthesia:**

To ensure proper analgesia during caudal blockade and avoid side effects, it is important to calculate the appropriate amount of local anesthetic. Factors such as body weight, height, age, and injection speed can affect the cranial spread of local anesthetics. Weight-based formulas have been traditionally used in pediatric regional anesthesia, but the desired reach of the block in terms of dermatomal level must also be considered. The volume of the epidural space increases continuously from caudal to cranial, with median volumes of 1.30, 1.57, and 1.78 ml/kg at the L1, T10, and T6 levels, respectively. Therefore, the well-established formula introduced by Armitage in 1979 is still recommended, where 0.5 ml/kg is expected to reach sacral, 1.0 ml/kg lumbar, and 1.25 ml/kg mid-thoracic dermatomes. The speed of injection of the local anesthetic does not affect its cranial spread in the caudal epidural space of infants and children. Complications such as significant changes in blood pressure are uncommon in pediatric patients after the accurate administration of epidural analgesia. A high sympathetic single-injection caudal block to T6 has been found to evoke no significant changes in heart rate, cardiac index, or blood pressure in children. Even when thoracic epidural block is combined with general anesthesia, cardiovascular stability is usually maintained in otherwise healthy pediatric patients. It is important to avoid performing test dosing when the child is in a very light plane of anesthesia or when there is stimulation, such as repositioning the patient **(30)**.

Bupivacaine

Bupivacaine is an amide local anesthetic that is widely used in clinical practice. It has a longer duration of action compared to other amide local anesthetics due to the addition of a four-carbon aliphatic side chain to the mepivacaine molecule, which increases its lipid solubility and protein binding.

Clinically, bupivacaine is used in concentrations ranging from 0.25% to 0.75%, with the intermediate concentration of 0.5% providing excellent anesthesia for peripheral nerves and in neuroaxial block **(31).**

Bupivacaine is commonly used for local or regional anesthesia, analgesia for surgery, dental procedures, diagnostic and therapeutic procedures, and obstetrical procedures. It is a potent local anesthetic that provides local anesthesia through the blockade of nerve impulse generation and conduction. Bupivacaine has along duration of action compared to other local anesthetics, but it is also the most toxic to the heart when administered in large doses **(32).**

Bupivacaine is a local anesthetic that has the following properties:Acceptable onset,Long duration of action,Profound conduction blockade and Tendency to preferentially block sensory fibers **(32).**

Bupivacaine is primarily metabolized in the liver via conjugation with glucuronic acid. The major metabolite of bupivacaine is 2,6-pipecoloxylidine, which is mainly catalyzed by the enzyme cytochrome P450 3A4. This suggests that bupivacaine is metabolized through oxidative pathways. The metabolism of bupivacaine occurs by N-dealkylation, leading to the formation of N-desbutyl bupivacaine **(32).**

Dexmedetomidine

Dexmedetomidine is a potent and highly selective alpha2 adrenoceptor agonist (α2– AR). It has sedative-hypnotic, anxiolytic, analgesic, anesthetic and sympatholytic effects**.** In comparison to clonidine, another α2 agonist used for hypertension treatment, dexmedetomidine has a significantly higher α2:α1 adrenoreceptor ratio of approximately 1600:1, making it primarily a sedative-anxiolytic **(33)**.

The elimination half-life of dexmedetomidine is 2 hours, whereas clonidine has an elimination half-life of 8 hours. Additionally, the distribution half-life of dexmedetomidine is 6 minutes. Dexmedetomidine undergoes biotransformation in the liver, and approximately 95% of its metabolites are excreted by the kidneys **(33)**.

The typical dosage of dexmedetomidine for procedural sedation is 1 mcg/kg, followed by a continuous infusion of 0.2 mcg/kg/h. Its onset of action is less than 5 minutes, and the peak effect is achieved within 15 minutes . The pharmacological effects of dexmedetomidine can be reversed by the α2-receptor antagonist atipamezole **(34).**

Pharmacodynamics:

Dexmedetomidine is a relatively selective alpha2 adrenoceptor agonist with a broad range of pharmacologic properties. **α2-AR** agonists produce clinical effects after binding to G-Protein-coupled **α2-AR**, of which there are three subtypes (α2A, α2B, and α2C) with each having different physiological functions and pharmacological activities. These receptor subtypes are found in the central, peripheral, and autonomic nervous systems, as well as in vital organs and blood vessels **(35)**.

It binds to the alpha2 receptors of locus ceruleus and spinal cord and causes sedation and analgesia respectively. Higher affinity to alpha2 receptors selectively leads to vagomimetic action on heart (bradycardia) and vasodilatation. The role as an anti-shivering agent and diuretic is yet to be established **(35)**.

Pharmacokinetics:

Intravenous dexmedetomidine exhibits linear pharmacokinetics with a rapid distribution half-life of approximately 6 minutes and a terminal elimination half-life of approximately 2 hours. Plasma protein binding of dexemedotomindine is about 94% (mostly albumin). Dexmedetomidine is metabolized by the liver via glucuronidation and cytochrome P450. As such, it should be used with caution in people with liver disease .The majority of metabolized dexmedetomidine is excreted in the urine (~95%) **(33)**.

Oral bioavailability is poor because of extensive first pass metabolism. However, after sublingual & intranasal administration bioavailability is high (84%), giving it a potential role in pediatric sedation and premedication. **(33)**.

It undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine (95%) and stool (4%) **(33)**.

Adverse effects:

The most frequently observed adverse effects include hypotension, hypertension, bradycardia, dry mouth and nausea. Other reported adverse effects include fever, rigors, cyanosis, muscle weakness. It may lead to arrhythmias, AV Block, cardiac arrest, T-wave inversion, tachycardia, angina pectoris, pulmonary edema, bronchospasm, respiratory depression, syncope, neuropathy, paresthesia, paresis, hyperkalemia, lactic acidosis and hyperglycemia **(33)**.

Tolerability of dexmedetomidine hydrochloride was noted in healthy subjects who achieved plasma concentrations from 1.8 up to 13 times the upper boundary of therapeutic range. The most notable effect

observed in those who achieved the highest plasma concentration was AV block which resolved spontaneously within one minute **(34).**

Dexmedetomidine has not been studied for its dependence potential in humans, but studies in rodents and primates have shown that abrupt discontinuation of the drug can result in a clonidine-like withdrawal syndrome. This syndrome is characterized by symptoms such as irritability, headache, and agitation, which may be accompanied or followed by a rapid rise in blood pressure and elevated catecholamine levels in the plasma. However, it is important to note that the specific antagonist Atipamezole can readily reverse the effects of dexmedetomidine, although this has only been evaluated in animals **(36).**

- **Drug interaction:**

Dexmedetomidine may enhance the effects of other sedatives and anesthetics when co-administered. Similarly, drugs that lower blood pressure and heart rate, such as beta blockers, may also have enhanced effects when co-administered with dexmedetomidine **(37).**

Clinical applications in anesthesia:

- Premedication:

Dexmedetomidine is used as a premedication due to its sedative, anxiolytic, analgesic, and sympatholytic properties, as well as its stable hemodynamics. It is known to decrease oxygen consumption during the intraoperative and postoperative periods. The recommended dose for premedication is 0.33-0.67 mg/kg IV or 2.5 μ **(38)**.

- Intensive care unit sedation:

Dexmedetomidine is a sedative drug can be used for initially intubated and mechanically ventilated patients during treatment in intensive care unit. It is approved by the FDA for use in the ICU for not more than 24 hours, although many studies have reported its safe use for longer durations **(6)**.

Several studies suggest that dexmedetomidine for sedation in mechanically ventilated adults may reduce time to extubation and ICU stay. Compared with other sedatives, some studies suggest that dexmedetomidine may be associated with less delirium **(39).**

- Procedural sedation:

Dexmedetomidine is a sedative drug that is indicated for the sedation of non-intubated patients prior to and/or during surgical and other procedures **(34).**

It has been safely used in various procedures such as trans-esophageal echocardiography, colonoscopy, awake carotid end-arterectomy, shockwave lithotripsy, vitreoretinal surgery, and pediatric tonsillectomy. The usual dose of dexmedetomidine for procedural sedation is 1μg/kg, followed by an infusion of 0.2μg/kg. Its onset of action is less than 5 minutes, and the peak effect occurs within 15 minutes **(40)** .

- As an adjuvant in local & regional techniques:

Highly lipophilic nature of dexmedetomidine allows rapid absorption into the cerebrospinal fluid and binding to alpha2-A receptors of spinal cord for its analgesic action. It prolongs the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration (e.g., epidural caudal or spinal). It enhances both central and peripheral neural blockade by local anesthetics and has been successfully used in intravenous regional anesthesia (IVRA). Addition of 0.5 μg/kg dexmedetomidine to lidocaine for IVRA improves quality of anesthesia and improves intraoperative-postoperative analgesia without causing side effects. The peripheral neural blockade is due to its binding to alpha2 A receptors. Dexmedetomidine added to levobupivacaine for axillary brachial plexus block shortens the onset time and prolongs the duration of the block and postoperative analgesia **(41)**.

Attenuation of response to tracheal intubation and extubation:

Dexmedetomidine attenuates hemodynamic stress response to intubation and extubation by its sympatholytic property. As respiratory depression is absent, it can be continued at extubation period unlike other drugs. Dexmedetomidine at IV doses of 0.33to 0.67 μg/kg given 15 min before surgery attenuates the hemodynamic response to endotracheal intubation **(40)** .

Precautions:

Continuous electrocardiogram **(ECG),** blood pressure and oxygen saturation monitoring are recommended during IV infusion of dexmedetomidine in preexisting severe bradycardia up to heart block or ventricular dysfunction (ejection fraction <30) including decompensated congestive heart failure. Hypovolemic patients need fluid supplementation because they are more prone to hypotension under dexmedetomidine therapy. Elderly and diabetics are more prone to hypotension as it decreases sympathetic nervous activity. However, dexmedetomidine may lack amnesic properties, as a small number of patients during the study were able to recall their ICU stay and found the experience very stressful **(42).**

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