Anestesia em Paciente com Insensibilidade Congênita a Dor e Anidrose *

*Anesthesia in a Patient With Congenital Insensitivity to Pain and Anhidrosis**

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RESUMO

Oliveira CRD, Paris VC, Pereira RA, Lara FST – Anestesia em Paciente com Insensibilidade Congênita a Dor e Anidrose.

***JUSTIFICATIVA E OBJETIVOS**: A insensibilidade congênita a dor e anidrose (ICDA) ou neuropatia hereditária sensorial e autonômica tipo IV (NHSA tipo IV) é neuropatia autossômica recessiva rara do grupo das neuropatias hereditárias sensoriais e autonômicas (NHSA), caracterizada por insensibilidade ao estímulo doloroso, anidrose e retardo mental. Existem poucos relatos sobre a conduta anestésica em pacientes com ICDA devido sua extrema raridade. O objetivo deste relato foi apresentar a conduta anestésica em paciente com ICDA submetida à artrodese de tornozelo esquerdo com colocação de haste e discutir as características de interesse para a anestesia nestes pacientes.*

***RELATO DO CASO**: Paciente com história de ICDA foi admitida para artrodese de tornozelo esquerdo devido à artropatia de Charcot. Na sala de operação foi monitorizada com eletrocardiógrafo, índice bispectral, SEF 95%, pressão arterial não invasiva e saturação periférica da hemoglobina, medicada com midazolam como pré-anestésico e submetida à anestesia venosa com propofol e cisatracúrio. Não houve a necessidade de administração de analgésicos. Após intubação traqueal, foi acrescentada monitorização da pressão expiratória final do gás carbônico e da temperatura esofágica. Não apresentou complicações no período perioperatório. Teve alta hospitalar no segundo dia de pós-operatório.*

***CONCLUSÕES**: Embora apresentem insensibilidade à dor, alguns pacientes apresentam hiperestesia tátil, o que poderia causar sensações desagradáveis durante a manipulação cirúrgica. Apesar de relatos na literatura de pacientes submetidos a bloqueios no neuroeixo e até mesmo a procedimentos sem anestesia, neste caso utilizou-se a anestesia venosa que proporcionou condições adequadas para o procedimento anestésico-cirúrgico.*

Unitermos: ANESTESIA, Geral: venosa; DOENÇAS, Congênita: neuropatia hereditária sensorial e autonômica, insensibilidade congênita à dor.

SUMMARY

Oliveira CRD, Paris VC, Pereira RA, Lara FST – Anesthesia in a Patient with Congenital Insensitivity to Pain and Anhidrosis.

***BACKGROUND AND OBJECTIVES:** Congenital insensitivity to pain and Anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV (HSAN IV) is a rare autosomal recessive neuropathy of the group of hereditary sensory and autonomic neuropathies (HSAN) characterized by insensitivity to pain, anhidrosis, and mental retardation. Since it is a rare condition, reports on the anesthetic conduct in patients with CIPA are not easily found in the literature. The objective of this report was to present the anesthetic conduct in a patient with CIPA undergoing left ankle arthrodesis with placement of an implant, and to discuss the characteristics of this disorder that concern anesthesiologists the most.*

***CASE REPORT:** A female patient with a history of CIPA was admitted for left ankle arthrodesis due to Charcot arthropathy. In the operating room, the patient was monitored with an electrocardiograph, bispectral index, 95% SEF, non-invasive blood pressure, and peripheral hemoglobin saturation; she was pre-medicated with midazolam and underwent intravenous anesthesia with propofol and cisatracurium. The administration of analgesics was not necessary. After tracheal intubation, monitoring of end-expiratory pressure of carbon dioxide and esophageal temperature were added. The patient did not develop postoperative complications. She was discharged from the hospital on the second postoperative day.*

***CONCLUSIONS:** Although there is insensitivity to pain, some patients present tactile hyperesthesia that can cause unpleasant feelings during surgical manipulation. Despite reports in the literature of patients undergoing neuroaxis blocks, and even procedures without anesthesia, intravenous anesthesia, which provided adequate conditions for the anesthetic-surgical procedure was used in this case.*

Keywords: ANESHTESIA, General: intravenous; DISEASES, Congenital: hereditary sensory and autonomic neuropathy, congenital insensitivity to pain.

INTRODUÇÃO

Descrita inicialmente por Swanson [1] em dois irmãos com alteração do controle da temperatura corporal e insensibilidade à dor, a insensibilidade congênita a dor e anidrose

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*Apresentado (**Submitted**) em 1 de dezembro de 2008*
*Aceito (**Accepted**) para publicação em 20 de maio de 2009*

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Anesthesia in a Patient with Congenital Insensitivity to Pain and Anhidrosis

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INTRODUCTION

Congenital insensitivity to pain and anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy (HSAN) type IV, initially described by Swanson[1] in two brothers with changes in temperature control and insensitivity to pain, it is a rare autosomal recessive neuropathy of the group of hereditary sensory and autonomic neuropathies (Table I), characterized by insensitivity to painful stimuli, changes in temperature control, and varying degrees of mental retardation. It is secondary to a mutation in the neurotrophic tyrosine kinase receptor type 1 (NTRK1) gene, located in chromosome 1. It encodes the tyrosine kinase receptor type A that is autophosphorylated in response to nerve growth factor (NGF) activating several intracellular signaling pathways. Mutations in the NTRK1 gene inhibit the development of NGF-dependent sensory and autonomic neurons during the embryonic period[2].

In adults, NGF is not necessary for cellular survival; however, it plays a crucial role in pain generation and hyperalgia in acute and chronic pain. The expression of NGF is increased in traumatized and inflamed tissues, and activation of tyrosine kinase receptor type A in nociceptive neurons potentiates pain through several mechanisms[3].

Insensitivity to pain and mental retardation causes those patients to self-mutilation (especially fingers, lips, and tongue), corneal lacerations, non-painful fractures, Charcot arthropathies, and joint deformities leading to chronic osteomyelitis and septic arthritis[4,5].

In a study conducted in Japan with 15 patients, they all presented some degree of tactile sensitivity or hyperesthesia. Thermal sensitivity varies, but most patients have some degree of cold and heat sensitivity[5].

The reduction in the central and peripheral activities of noradrenaline and anhidrosis can lead to the development of perioperative hypotension and hyperthermia[4,5].

The diagnosis of CIPA is based on the clinical presentation, pharmacological test (intradermic reaction to 1:10,000 histamine), and neuropathological exam: absence of unmyelinated fibers (C fibers), reduction in the number of small myelinated fibers (Aδ fibers), and normal distribution of large myelinated fibers (Aα and Aβ fibers). The structure of the sweat glands is normal but they are not innervated. Genetic analysis looking for mutations on the NTRK1 gene represents the last diagnostic step[4].

Specific treatment is not available and due to the high morbidity associated with this disorder patients usually do not live past the second decade of life.

There are very few reports of anesthesia in patients with this disease, which is very rare but it is related with some ethnic groups and consanguinity[6,7].

The objective of this report was to present the anesthetic conduct in a patient with CIPA undergoing left ankle arthrodesis with placement of an implant and to discuss the characteristics that might be of interest to anesthesia.

CASE REPORT

This is a 24 years old female weighing 82 kg, 153 cm height, with a history of CIPA who was admitted for the surgical treatment of Charcot arthropathy in the left ankle. She was scheduled for left ankle arthrodesis with placement of an implant. Her family members reported a history of consanguinity (her parents were cousins) and that the patient had two brothers, one younger with the same characteristics, and a brother who died as a child. Preoperative laboratorial exams were within normal limits.

The patient was not taking any drugs and this was her second surgery. The first surgery, also orthopedic, was an

Table I – Classification of Hereditary Sensory and Autonomic Neuropathies

HSAN	Onset	Inheritance	Neurons (axons)			Anhidrosis	Loci	Gene
			Aα	Aδ	C			
Type I	2nd decade	AD	+	++	++	LS	9p22	SPTLC1
Type II	Congenital	AR	++	++	+	G	Unknown	Unknown
Type III	Congenital	AR	++	++	++	G	9p31	IKBKAP
Type IV	Congenital	AR	N	+	++	G	1q21	NTRK1
Type V	Congenital	AR	N	N/+	N/+	G	Unknown	Unknown

AD - autosomal dominant; AR - autosomal recessive; N - normal; **+**: affected; **++**: severely affected; LS - lumbosacral; G - Generalized.
Dyck PG - Diseases of Peripheral Nerves, In: Engel AG, Franzini-Armstrong C - Myology. 2nd ed. New York, McGraw Hill, 1994.

intervention in the lower limbs under subarachnoid block, two years ago, without intercurrences[8].

On physical exam she had a short neck, macroglossia, and Mallampati III indicating the possibility of difficult airways. She was obese, had diffuse lack of sensitivity to pain, and self-induced injuries in hands and distal extremities of the finger (Figure 1). The patient was calm, oriented, and seemed to be mentally impaired in relation to her chronological age.

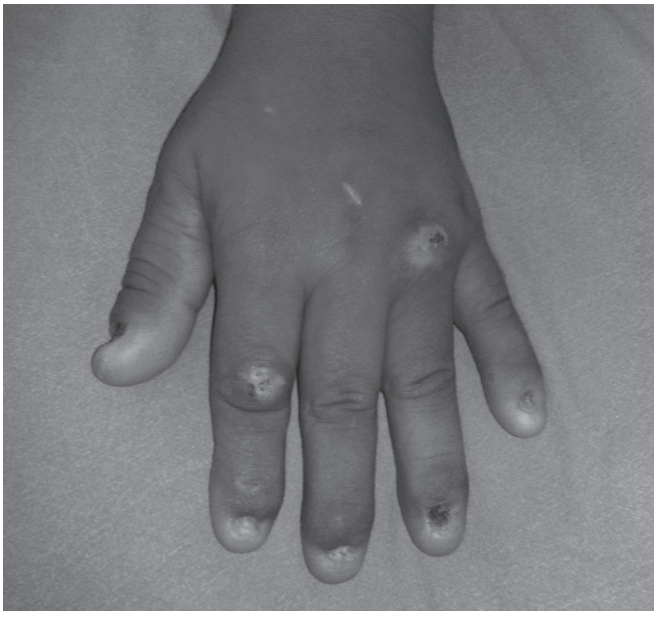

Figure 1 – Self-Inflected Lesions.

Upon arrival to the operating room, monitoring with electrocardioscope (ECG) on D_{II} and V_5 derivations, peripheral hemoglobin saturation (SpO_2), bispectral index, spectral edge frequency 95% (SEF 95), and non-invasive blood pressure (NIBP) with intermittent measurements was instituted; baseline parameters were within normal limits. An 18G catheter was used for venipuncture in the left upper limb without complaints of discomfort.

After venipuncture, the patient received midazolam (5 mg) and anesthetic induction was initiated with 100% oxygen (2 $L.min^{-1}$) under a face mask, target-controlled infusion of 2% propofol at 4.0 $\mu g.L^{-1}$ for four minutes, followed by the administration of cisatracurium (a bolus of 0.2 $mg.kg^{-1}$ when the bispectral index reached 45). A 7.5-mm ET tube with balloon was used for tracheal intubation. Monitoring of end-expiratory pressure of carbon dioxide ($P_{ET}CO_2$) and esophageal temperature was added. Although laryngoscopy and intubation were not difficult, a discrete elevation in blood pressure and heart rate was also observed (Figure 2). Controlled ventilation with an inspired oxygen fraction (FiO_2) of 0.5 was instituted, and anesthesia was maintained with target-controlled infusion of propofol that ranged from 2.0 to 3.0 $\mu g.mL^{-1}$ until 10 minutes before the end of the surgery, when the infusion of propofol was discontinued. Opioids were not used and additional doses of the neuromuscular blocker were not required. The patient was extubated after the 120-minute long procedure and she was transferred to the post-anesthetic care unit (PACU) with monitoring and receiving oxygen via a nasal cannula (2 $L.min^{-1}$) without complaints.

The temperature of the patient remained stable during the procedure. The room temperature was maintained between

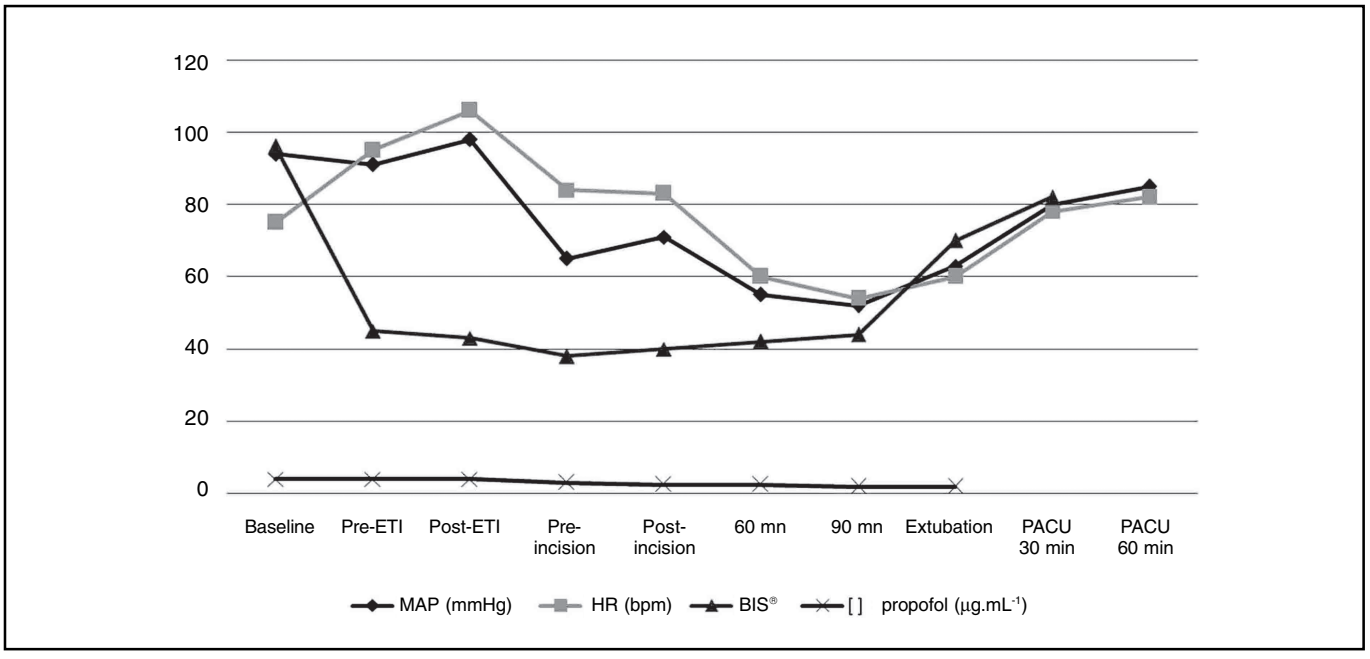

Figure 2 – Main Parameters and Intraoperative Variation.

22° and 24° C. A thermal mattress was placed before the surgery, but its use was not necessary during the procedure. The patient was discharged from the hospital after two days, and during that period she did not require any analgesics.

DISCUSSION

Patients with CIPA have autonomic and nociceptive dysfunction; therefore, the anesthetic conduct represents a challenge for the anesthesiologist.

In a review of the literature, some important aspects of those patients are emphasized, especially in relation to the type of anesthesia and perioperative temperature control[9].

Although those patients have insensitivity to pain, some of them have tactile hyperesthesia, which can cause an uncomfortable perception during surgical manipulation[10,11].

Perception of tactile stimuli and pressure can also cause complaints of postoperative pain.

There are reports of surgical procedures without anesthesia in patients with CIPA, such as the case of a patient who underwent amputation of both feet under sedation, but without analgesia. He did not show any response to incision of the skin or disarticulation, and he only reacted to clamping of a nerve trunk with flexion of a limb[12].

An eight-year old patient with CIPA underwent reduction of a femur fracture with osteosynthesis under epidural block and sedation without complications during the procedure[13].

Although patients with CIPA have low plasma concentrations of adrenaline and noradrenaline, cardiovascular reflexes are preserved. However, several patients have hemodynamic instability due to sepsis secondary to severe infectious disorders, such as osteomyelitis and septic arthritis[4,9].

The use of epidural blocks in Riley Day syndrome (familial dysautonomy or hereditary sensory and autonomic neuropathy type III) characterized by autonomic dysfunction has been reported. Epidural block combined with general anesthesia was used in three patients undergoing Nissen fundoplicature. All patients remained hemodynamically stable[14].

In the presence of anhidrosis, the regulation of body temperature fails, causing recurrent episodes of fever, and 20% of those patients die of hyperthermia in the first three years of life[4]. The elevation of the temperature can be prevented by adequate monitoring, adjusting the temperature of the operating room, and using thermal mattresses. The association between CIPA and malignant hyperthermia has not been reported.

Due to the varying phenotypical expression, mental retardation can range from mild to severe, but some patients are described as apparently normal[15,16]. In this case, neuroaxis block with mild sedation can be used, but general anesthesia is the technique of choice in patients with severe mental impairment[17,18].

In a case report, a patient with CIPA was maintained with low concentrations of sevoflurane without analgesics during general anesthesia for an orthopedic surgery without intercurrences. The patient had a fast arousal without complaining of pain. The serum levels of antidiuretic hormone, cortisol, and catecholamines were measured before, during, and after the procedure, showing negligible elevations during the procedure[19].

The patient should be carefully place on the surgical table, whose surface should be padded to prevent pressure injury and reduce the risk of new traumas secondary to involuntary movements during awakening[5,20].

The development of corneal damage is favored by the insensitivity and imprudence characteristic of children who do not have the repressive stimulus of pain. Special emphasis is placed on the work of the ophthalmologist in trying to avoid complete blindness[20,21].

Although the patient presented here had predictive indexes of difficult airways, laryngoscopy and tracheal intubation were done without difficulties. However, it is prudent to have alternatives to access the airways, as well as the presence of a second anesthesiologist in the operating room.

The elevation in the blood pressure and heart rate during manipulation of the airways were secondary to the integrity of airways reflexes; however, extubation was not associated with the same changes (Figure 2).

Bispectral encephalography (Bispectral index and SEF 95) represented an important intraoperative monitoring tool, remaining stable and showing adequate levels of hypnosis during the entire procedure.

The patient did not require the intra- and postoperative use of analgesics, and the anesthetic plane was maintained with a hypnotic agent in doses similar to those used in the general population with minimal cardiovascular manifestations during laryngoscopy, intubation, and surgical incision.

The psychosocial impact on the patient and family members is as important as the anesthetic-surgical aspect of the disease, since those patients may require frequent surgeries. Progression of the disease is associated with several limitations of activities of daily living since childhood, requiring parents to be extremely attentive and careful. Thus, a careful pre-anesthetic evaluation is mandatory to decrease the anxiety and emotional stress of those patients.

REFERÊNCIAS – *REFERENCES*

01. Swanson AG - Congenital insensitivity to pain with anhidrosis. A unique syndrome in two male siblings. Arch Neurol, 1963;8:299-306.
02. Indo Y, Tsuruta M, Hayashida Y et al. - Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet, 1998;13:485-488.
03. Hefti FF, Rosenthal A, Walicke PA et al. - Novel class of pain drugs based on antagonism of NGF. Trends Pharmacol Sci, 2006;27:85-91.
04. Rosemberg S, Marie SKN, Kliemann S - Congenital insensitivity to pain with anhidrosis (Hereditary sensory and autonomic neuropathy type IV*).* Pediatr Neurol, 1994;11:50-56.
05. Tomioka T, Awaya Y, Nihei K et al. - Anesthesia for patients with congenital insensitivity to pain with anhidrosis: a questionnaire study in Japan. Anesth Analg, 2002;94:271-274.

06. Shatzky S, Moses S, Levy J et al. - Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: genetic heterogeneity, novel mutations in the TRKA/NGF receptor gene, clinical findings, and results of nerve conduction studies. Am J Med Genet, 2000;92:353-360.
07. Karkashan EM, Joharji HS, Al-Harbi NN - Congenital insensitivity to pain in four related Saudi families. Pediatr Dermatol, 2002;19: 333-335.
08. Oliveira CRD, Santos FA, Nogueira CS et al. - Spinal anesthesia in a patient with congenital insensitivity to pain with anhidrosis. Anesth Analg, 2007;104:1561-1562.
09. Kao SC, Ting CK, Cheng KW et al. - Desflurane used in a patient with congenital insensitivity to pain with anhidrosis during septic shock. J Chin Med Assoc, 2004;67:305-307.
10. Okuda K, Arai T, Miwa T et al. - Anesthetic management of children with congenital insensitivity to pain with anhidrosis. Pediatr Anaesth, 2000;10:545-548.
11. Rozentsveig V, Katz A, Weksler N et al. - The anaesthetic management of patients with congenital insensitivity to pain with anhidrosis. Paediatr Anaesth, 2004;14:344-348.
12. Layman PR - Anaesthesia for congenital analgesia. A case report. Anaesthesia, 1986;41:395-397.
13. Rodriguez Pérez MV, Fernandes Daza PL, Cruz-Villaseñor JA et al. - Anestesia epidural a un niño con fractura de fémur e insensibilidad congénita al dolor. Rev Esp Anestesiol Reanim, 2002;49:555-557.
14. Challands JF, Facer EK - Epidural anaesthesia and familial dysautonomia (the Riley Day syndrome). Three case reports. Paediatr Anaesth, 1998;8:83-88.
15. Nagasako EM, Oaklander AL, Dworkin RH - Congenital insensitivity to pain: an update. Pain, 2003;101:213-219.
16. Mitaka C, Tsunoda Y, Hikawa Y et al. - Anesthetic management of congenital insensitivity to pain with anhidrosis. Anesthesiology, 1985;63:328-329.
17. Haworth AE, Thomas NH, Cook LJ et al. - Hereditary sensory and autonomic neuropathy with anhidrosis (type IV). J R Soc Med, 1998;91:84-86.
18. Thakur LC, Chandran V, Anand KS - Congenital sensory neuropathy with anhidrosis. Indian Pediatr, 1992;29:1046-1048.
19. Yoshitake S, Matsumoto K, Miyagawa A et al. - Anesthetic consideration of a patient with congenital insensitivity to pain with anhidrosis. Masui, 1993;42:1233-1236.
20. Trope GE, Jay JL, Dudgeon J et al. - Self-inflicted corneal injuries in children with congenital corneal anaesthesia. Br J Ophthalmol, 1985;69:551-554.
21. Amano S, Fukuoka S, Usui T et al. - Ocular manifestations of congenital insensitivity to pain with anhidrosis. Am J Ophthalmol, 2006;141:472-477.

RESUMEN

Oliveira CRD, Paris VC, Pereira RA, Lara FST – Anestesia en Paciente con Insensibilidad Congénita al Dolor y Anhidrosis.

JUSTIFICATIVA Y OBJETIVOS*: La falta de sensibilidad congénita al dolor y la anhidrosis (ICDA) o neuropatía hereditaria sensorial y autonómica tipo IV (NHSA tipo IV), es una neuropatía autosómica recesiva rara del grupo de las neuropatías hereditarias sensoriales y autonómicas (NHSA), caracterizada por la insensibilidad al estímulo doloroso, anhidrosis y retraso mental. Existen pocos relatos sobre la conducta anestésica en pacientes con ICDA, debido a su extrema raridad. El objetivo de este relato, fue presentar la conducta anestésica en paciente con ICDA sometida a la artrodesis de tobillo izquierdo con colocación de vástago y discutir las características de interés para la anestesia en esos pacientes.*

RELATO DEL CASO*: Paciente con historial de ICDA que fue admitida para artrodesis de tobillo izquierdo debido a la artropatía de Charcot. En la sala de operación, fue monitorizada con electrocardiógrafo, índice bispectral, SEF 95%, presión arterial no invasiva y saturación periférica de la hemoglobina, y medicada con midazolam como preanestésico. Posteriormente fue sometida a anestesia venosa con propofol y cisatracurio. No hubo necesidad de administrar analgésicos. Después de la intubación traqueal, se le monitoreó la presión expiratoria final del gas carbónico y de la temperatura esofágica. No presentó complicaciones en el período perioperatorio. Obtuvo su alta al segundo día del postoperatorio.*

CONCLUSIONES*: Aunque presenten insensibilidad al dolor, algunos pacientes debutan con hiperestesia táctil, lo que podría causar sensaciones desagradables durante la manipulación quirúrgica. A pesar de los relatos en la literatura de pacientes sometidos a bloqueos en el neuro eje, e incluso a procedimientos sin anestesia, en ese caso se usó la anestesia venosa, proporcionando condiciones adecuadas para el procedimiento anestésico-quirúrgico.*