Compassionate use of medicinal *Cannabis* for pain treatment in children with Klippel-Trenaunay Syndrome. Case report

Uso compassivo de Cannabis medicinal para tratamento de dor em criança com Síndrome de Klippel-Trenaunay. Relato de caso

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ABSTRACT

BACKGROUND AND OBJECTIVES: Klippel-Trenaunay syndrome (KTS) is a rare congenital disease that manifests at birth or in childhood and has an unknown etiology, with no ethnic or gender predilection. Pain management, common in many cases, is challenging due to the complexity of the factors involved. The aim of this report is to demonstrate the effective use of a multimodal approach, including medicinal cannabis, in the treatment of pain in a child with KTS.

CASE REPORT: this is the case of a child suffering from CTS who had severe chronic pain, significantly compromising his quality of life. The pain was managed with pharmacological therapies, including the use of medicinal cannabis as a therapeutic alternative when conventional treatments proved insufficient. The multimodal approach, which included the use of tetrahydrocannabinol, led to a reduction in pain and an improvement in the patient's quality of life. Medical cannabis therapy proved to be an effective option, especially in cases of pain refractory to other interventions.

CONCLUSION: The treatment of pain in patients with KTS should be multimodal, with an emphasis on non-invasive approaches. The use of medicinal cannabis is a viable and safe alternative, particularly in situations where conventional treatments do not provide adequate relief.

Keywords: analgesic pain management, cannabidiol, chronic pain, medicinal cannabis, tetrahydrocannabinol.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A síndrome de Klippel-Trenaunay (KTS) é uma doença congênita rara que se manifesta no nascimento ou na infância e apresenta etiologia desconhecida, sem predileção étnica ou de gênero. O manejo da dor, comum em muitos casos, é desafiador devido à complexidade dos fatores envolvidos. O objetivo deste relato foi demonstrar o uso eficaz de uma abordagem multimodal, incluindo cannabis medicinal, no tratamento da dor em uma criança com KTS.

RELATO DO CASO: Trata-se do caso de uma criança portadora de KTS que apresentava dor crônica intensa, comprometendo significativamente sua qualidade de vida. A dor foi manejada com terapias farmacológicas, incluindo uso de cannabis medicinal como alternativa terapêutica, quando os tratamentos convencionais se mostraram insuficientes. A abordagem multimodal, que incluiu o uso de tetraidrocanabinol, levou à redução da dor e à melhora na qualidade de vida do paciente. A terapia com cannabis medicinal demonstrou ser uma opção eficaz, especialmente em casos de dor refratária a outras intervenções.

CONCLUSÃO: O tratamento da dor em pacientes com KTS deve ser multimodal, com ênfase em abordagens não invasivas. O uso de cannabis medicinal é uma alternativa viável e segura, particularmente em situações em que tratamentos convencionais não proporcionam alívio adequado.

Descritores: canabidiol, cannabis medicinal, dor crônica, manejo analgésico da dor, tetraidrocanabidiol.

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HIGHLIGHTS

- A multimodal approach, including medical *Cannabis*, was effective in controlling pain in pediatric patients with Klippel-Trenaunay Syndrome.
- The use of tetrahydrocannabinol provided significant pain relief and improved quality of life after other therapies had failed.
- The management of opioids represents a challenge in non-cancer pain, reinforcing the importance of alternatives such as medical *Cannabis* for the safe control of chronic pain.

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INTRODUCTION

Klippel-Trenaunay syndrome (KTS) is defined as a complex congenital disorder resulting from venous and capillary malformations associated with limb growth[1]. It is a rare disease resulting from a mutation in the PIK3CA, gene that presents at birth or in infancy, with unknown incidence and prevalence, without ethnic or gender predilection. Its etiology is still not understood, although some theories have been postulated, such as paradominant inheritance, somatic mosaicism of a dominant lethal gene, altered embryonic vasculogenesis and mesodermal defects[2]. The diagnosis is eminently clinical, associated with imaging tests, such as magnetic resonance imaging[3]. From a clinical point of view, port wine stains are observed and can be seen from birth, being more common on the lower limbs which represent 95% of cases, with an incidence of 11% in the upper limbs, both in isolation and on one side only[4].

In a study involving 252 patients diagnosed with this syndrome, it was found that 37% of them reported pain[5]. The presence of pain causes a reduction in quality of life and determines a significant increase in morbidity among patients. Pain management is a challenge in the treatment of these patients. Therefore, a multimodal approach is recommended, with non-invasive interventions being more effective than surgical ones for the treatment of vascular lesions and bone masses[6]. In this context, the use of medicinal cannabis should be considered as a viable therapeutic alternative, especially when conventional options prove insufficient. This report aims to demonstrate the efficacy of medicinal cannabis in the treatment of pain in children undergoing non-oncological pediatric palliative care.

CASE REPORT

This case report took into account a male patient with KTS with a history of multiple hospitalizations and approaches, including embolic treatment of vascular lesions at seventeen and at forty-three days of life.

At two months of age, he was treated with sirulimus, with the objective of controlling vascular lesions, which were predominant in the left lower limb (Figure 1). He took the drug for two years, but this was suspended due to lesion control. He underwent a vesicostomy, and then followed a ureterostomy due to a neurogenic bladder, complicated by multiple urinary tract infections.

On examination, the patient presented an extensive vascular lesion measuring 26.5cm at the largest circumference, Port-wine in color, on the left lower limb (Figure 2). In addition, there was the presence of a palpable mass on the left back and thoracolumbar scoliosis. Imaging tests showed intra-abdominal arteriovenous malformations and thoracic bone mass.

The patient was being treated for pain in the lower back and lower limbs orally and at home, using dipyrone 1g every 6 hours, amitriptyline 12.5mg, gabapentin 300mg every 20h, clonidine 0.050mg every eight hours, methadone 5mg every six hours and morphine rescue orally 10mg every four hours, (weight: 17kg - SC 0.72m²). He received outpatient care with pediatrics, neurology, pediatric surgery, urology and palliative care.

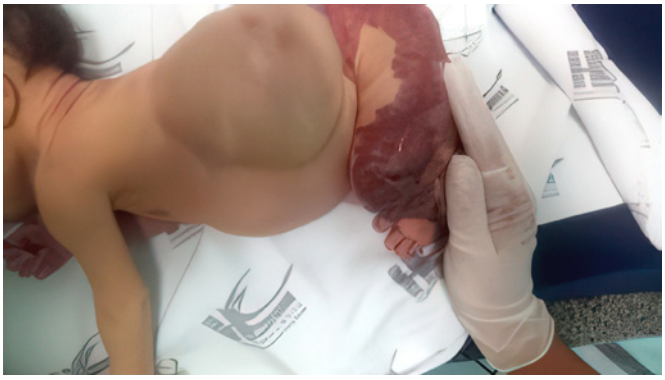

Figure 1. Port wine lesion on the left lower limb and abdominal mass present at birth

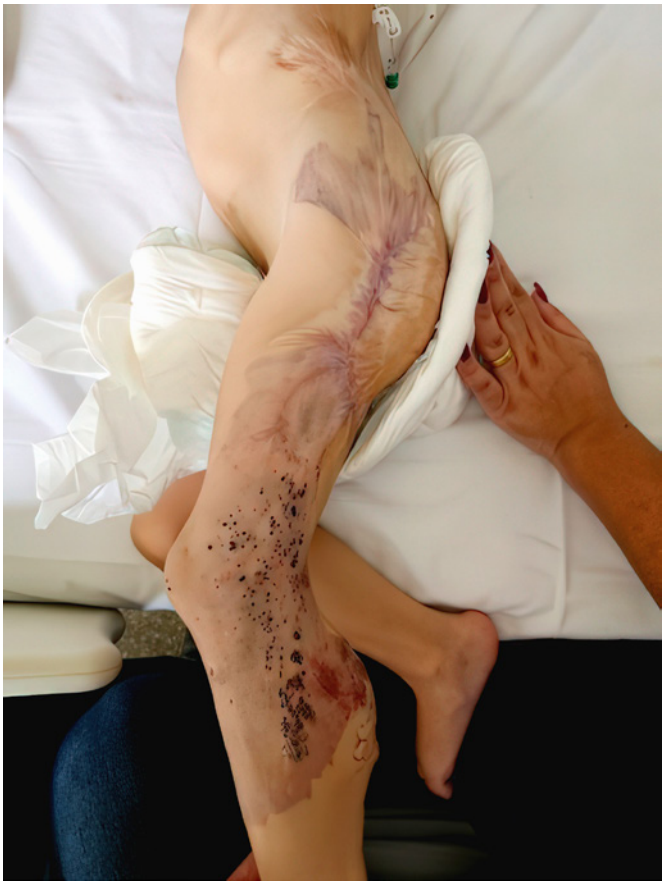

Figure 2. Lesions and scars on the left lower limb and left back at 5 years of age

At the age of five, the pain worsened, with complaints of pain in the dorsal region, left thoracolumbar region and left lower limb, of a continuous nature, strong in intensity, and without improvement with analgesics. A propaedeutic revealed, in nuclear magnetic resonance images, an increase in vascular lesions in the lower limbs and new intra-abdominal arteriovenous malformation, associated with growth of the previously existing thoracic bone mass.

Monitoring by the pain medicine team began, with pain assessment performed using the Face, Legs, Activity, Cry, Consolability (FLACC) Scale. This tool was selected due to the impossibility of verbal communication by the patient. The scale varied from 7 to 10 throughout the day, worsening at night and impacting on sleep, with optimization of analgesic therapy: gabapentin 900mg per day, methadone 21mg per day, orally, and morphine 3mg intravenously up to every six hours as pain rescue therapy. In addition, sirolimus was once again utilized. Despite pharmacological adjustment, the patient continued with uncontrolled pain, requiring several rescue doses of morphine on a daily basis. After multidisciplinary discussion, it was decided to insert an epidural catheter for infusion of a local anesthetic and opioid solution. Epidural analgesia was maintained for five days using 0.15% ropivacaine + 10μg/mL morphine with an infusion rate of 1mL per hour. An improvement in the pain was observed, with FLACC ranging from 3 to 5 throughout the day. The patient was discharged from hospital after twenty days with mild pain and using oral analgesic therapy including methadone 15mg per day, gabapentin 900mg per day, amitriptyline 12.5m per night, dipyrone 4g per day and morphine 10mg as rescue therapy.

The patient was readmitted after 6 months with nausea and vomiting associated with difficulty using oral drugs and experiencing intense pain crises, FLACC from 8 to 10. An optimized oral analgesia and antiemetic therapy was given, without good response, with treatment being changed to intravenous administration with methadone 15mg per day and maintenance of other drugs. Over the next twenty-four hours, he developed excessive drowsiness and desaturation, with the diagnostic hypothesis being opioid intoxication. He was kept under surveillance in the Intensive Care Unit, the opioid was suspended for twenty-four hours, and the dose of methadone was adjusted to 7.5mg per day on the following day, with improvement in the symptoms described. Ketamine infusion was started at night at 0.1mg/kg/h for six hours over a five-day period, leading to satisfactory analgesia, FLACC from 3 to 5, and an improvement in sleep quality.

Considering the failure of the oral treatments administered, cannabinoid therapy was initiated with the aim of not making any further increases in the opioid dose. THC 1mg at night was started with dose progression over seven days until the final dose of 4.5mg per day, resulting in good analgesic response, and an improvement in the child's sleep and daily activities.

Multimodal analgesia with medicinal cannabis was continued for 3 months, and was reassessed on an outpatient basis, maintaining FLACC from 3 to 5.

DISCUSSION

KTS, also known as angio-osteohypertrophy syndrome or hemangiectatic hypertrophy, is a rare pathology characterized by the triad: dermatological changes (flat angioma with "port wine" stains), bone deformities (limb overgrowth) and low-flow lymphatic or vascular malformations[2]. The existence of three indicators is present in around 63% of cases, while the presence of two of these characteristics corresponds to 37%[6].

The flat angioma is a dermatological change resulting from KTS that is present from birth and tends to increase in size with the individual's development and growth[7]. The capillary malformations can affect various organs, such as the heart, lungs, liver, kidney, gastrointestinal and genitourinary systems and bones, leading to compromised local and systemic homeostasis, and thus causing pain. Lymphatic malformations and the risk of thromboembolic conditions, such as superficial phlebitis and pulmonary embolism, are present in 19% to 40% of cases[7], and can present with associated painful conditions. Coagulation disorders limited to areas of vascular ectasia and dilated pelvic vessels, responsible for venous stasis, are also present, resulting in an increased risk of deep vein thrombosis. When present, lymphatic malformation results in chronic lymphedema and may lead to recurrent infections and ulcers. Hypertrophy of the affected limbs develops mainly in the subcutaneous and muscular tissue, with its evolution being unpredictable[8]. This overgrowth generates a compensatory balance of the pelvis and secondary scoliosis, in addition to functional limitations and chronic pain, with significant impairment in the quality of life of affected individuals. Studies show that painful conditions can be present in around 37% and can affect up to 88% of people with the disease[5,9]. The pathophysiology of pain in KTS is not yet completely elucidated. However, it is believed that eight main factors are responsible for the development of pain, namely: cellulitis, thrombophlebitis, deep vein thrombosis, calcification of vascular malformations, growth of bone masses, intraosseous vascular malformations, arthritis and neuropathic pain. Therefore, it is assumed that its pathophysiology is multifactorial[9]. A case report[6] suggested that the treatment of pain should be multimodal, aiming to control neuropathic and nociceptive pain, with non-invasive treatments, using drugs and anesthetic blocks, thus being superior to surgical approaches to vascular lesions and bone masses.

In the case reported here, the findings suggested multifactorial pain, with a suspected lumbar neuropathic component, associated with an inflammatory process resulting from the underlying disease. Therefore, a multimodal treatment was carried out using four classes of drugs: simple analgesics, gabapentinoids, antidepressants and opioids. Multimodal therapy has been established as an effective approach in pain management in pediatrics, integrating the use of multiple drugs with complementary mechanisms of action and non-pharmacological interventions to potentialize pain relief and reduce collateral effects associated with the isolated use of a single class of analgesics[10,11].

Methadone is an opioid agonist that also acts on NMDA receptors, promoting inhibition of serotonin and norepinephrine reuptake, and playing a role in the context of neuropathic pain[12]. The clinical picture of opioid intoxication includes a spectrum of signs and symptoms that can be life-threatening, including acute respiratory failure, which can be serious and even fatal[13]. The need for progressive increases in opioids in dramatic cases of pain like this may occur due to the development of tolerance or the evolution of the underlying disease. In the case reported here, the dose of methadone was high considering the child's age and weight, and when it was converted to an intravenous route, there was no adjustment of the equivalence of the oral route to

the intravenous route. The adverse effects associated with the use of opioids should lead to reconsideration of their use in patients suffering from non-cancer related pain.

Studies involving chronic pain and the use of epidural catheters for pain management in pediatric patients with KTS are scarce. Most articles involve post-surgical patients, whose acute pain management is necessary. These studies demonstrated pain relief with analgesia performed through continuous infusion, via the epidural route[14]. Recently, there has been increasing interest in the use of ketamine in pediatrics. It is a non-competitive antagonist of N-methyl-d-aspartate (NMDA) receptors and acts by reducing excitatory pathways[14]. Its use in pediatrics has been widely accepted due to its favorable safety profile and efficacy[16,17] and should be considered in the context of difficult-to-control chronic pain and pediatric palliative care[17-19].

Although cannabis has been used for analgesia since antiquity, its clinical use declined significantly in the first decades of the 20th century due to gaps in scientific knowledge, recreational abuse, and adverse effects[19]. The identification of the chemical structure of cannabis components and the isolation of pure constituents has been associated with a significant increase in scientific interest in the plant since 1965[20]. The classification of delta-9-tetrahydrocannabinol (THC) as the main psychoactive component and the subsequent isolation of cannabinoid receptors 1 and 2 (CB1 and CB2) led to an explosion of studies in the 1990s, with the identification of an endogenous cannabinoid system in the brain[20]. The endocannabinoid system (ECS) consists of endogenous cannabinoids (endocannabinoids - eCBs), cannabinoid receptors, enzymes responsible for the synthesis and degradation of eCBs, and all genes related to them[19].

cannabis contains hundreds of compounds, including terpenes, flavonoids, and unique compounds called phytocannabinoids. The two main phytocannabinoids are cannabidiol (CBD) and THC[21]. Cannabinoids interact with CB1 and CB2 receptors, which are linked to inhibitory G proteins and have significant expression in the nervous system. Cannabinoids act on CB1 and CB2 receptors improving mood, anxiety, immune function and reducing inflammation[21]. They exert antinociceptive effects both in the central and in the peripheral nervous system. The first receptor is present, in greater quantity, in the brain and in the periphery. It is presumed that CB1 acts as a modulator of excessive excitability of neurons, targeting several neurotransmitters, such as norepinephrine, serotonin, dopamine, GABA, glutamate and acetylcholine. CB2 receptors are more representative in the hematopoietic and immune systems, acting mainly in the modulation of chemical messengers of the immune system[22].

THC and CBD are the two most studied and well-known cannabinoids. THC is a CB1 and CB2 partial agonist, while CBD has low affinity for these receptors and has anti-inflammatory and antispasmodic benefits[21]. Despite recent evidence of its efficacy in treating pain in adults, research in children and adolescents is still limited. Currently in pediatrics, only pure CBD has a specific indication for refractory epilepsy[24]. Therefore, prescribing medicinal cannabis to children and adolescents requires caution[24].

One study evaluated and followed six patients in palliative care for one year, who had chronic pain refractory to conventional therapies. These patients received cannabinoids for pain management and presented conflicting results[22]. The authors recommended careful use and dose titration to safely achieve the therapeutic range[22]. Another study showed an improvement in pain scores in a sample of 21 children and suggested that cannabis can be used compassionately, as an adjuvant in analgesic treatment, in children with resistant chronic pain[26].

Despite promising results, the pharmacokinetics of CBD and THC in children are still little understood. Interindividual variability in exposure to these substances is high, and factors such as age, weight, and enzymatic maturation significantly influence drug absorption, distribution, metabolism, and excretion[21].

Another issue that deserves debate concerns the long-term impacts of cannabinoids on children. Previous research has indicated risks such as decreased ability to concentrate, dependence, cognitive decline, and schizophrenia. However, these studies have mostly been based on observation of recreational cannabis users over time[21,24]. The risk is particularly high among those who started using cannabis at an earlier age and in the presence of other risk factors, such as a family history of schizophrenia and concomitant consumption of alcohol and tobacco[22,24].

Public interest in cannabis-based treatments is on the rise, especially in relation to diseases that present demands as yet unmet, such as chronic pain. One of the factors responsible for the limited scientific arsenal is the heterogeneity in treatment, given the different formulations available and the lack of long-term follow-up of patients. It is essential to share advances, improvements and lessons learned with the scientific community. Cannabinoids, by acting on CB1 receptors, mainly promote the inhibition of pain perception, which is particularly useful in the management of chronic pain. On the other hand, the stimulation of CB2 receptors is linked to the anti-inflammatory effect.

CONCLUSION

Pain can affect up to 88% of patients with KTS, causing serious consequences to the functionality and quality of life of these individuals. For analgesic treatment of these patients to be more effective, the first step is to recognize the sources of pain, and then develop a multimodal and individualized treatment strategy, with cannabis being an option to be considered in cases where other available therapies have failed. However, more studies are needed to improve pain management with cannabis in the pediatric population.

AUTHORS' CONTRIBUTIONS

Michelle dos Santos Severino Costa
Conceptualization, Project Management, Research, Methodology, Writing - Review and Editing
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Data Collection, Research, Writing - Preparation of the Original

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Project Management, Research, Methodology, Supervision

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