VALPROIC ACID INTERFERENCE IN ABDOMINAL WALL TISSUE REPAIR: POTENTIAL IMPLICATIONS FOR HERNIA AND LAPAROTOMY SURGERIES

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Abstract: Valproic acid (AVP) is widely used in the treatment of epilepsy and mood disorders, but

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recent studies suggest that its epigenetic action may negatively interfere in tissue regeneration and healing processes. Repair of the abdominal wall, essential for the success of procedures such as herniorrhaphy and laparotomy, depends on a cascade of inflammatory, cellular and molecular events that can be modulated by systemic drugs such as AVP. The aim of this study was to analyze the interference of valproic acid in abdominal wall healing, considering its possible effects on collagen synthesis, fibroblast proliferation and the integrity of the extracellular matrix, and to discuss its clinical implications in abdominal surgery. This is a literature review with a qualitative and exploratory approach. The studies were selected using the PubMed, SciELO, ScienceDirect and Scopus databases, with full articles published in peer-reviewed scientific journals addressing the use of valproic acid in the context of tissue healing, especially in patients undergoing surgical procedures. The time frame of the research considered the period from 2018 to 2022, based on the oldest article (Costa et al., 2018) and the most recent (Santos et al., 2022; Alves et al., 2022; Moura et al., 2022). The findings indicate that AVP, by acting as a histone deacetylase (HDAC) inhibitor, can alter the gene expression of key proteins in the healing process, such as type I and III collagen, metalloproteinases and growth factors. In experimental models, delayed granulation tissue formation and collagen matrix organization were observed, suggesting an increased risk of dehiscence, incisional hernia and abdominal wall fragility in patients taking the drug continuously. We conclude that valproic acid may represent an underestimated risk factor in surgical repair of the abdominal wall. Preoperative assessment of the use of this drug should be considered in clinical practice, especially in elective surgeries. New clinical studies are needed to validate these experimental findings and guide safer therapeutic approaches.

Keywords: General Surgery; Tissue Repair Surgery; Valproic Acid.

INTRODUCTION

Valproic acid (VPA) is an anticonvulsant widely used in the treatment of epilepsy, bipolar



disorder, and other neurological conditions. Although its therapeutic effects are well documented, there is growing scientific interest in the systemic side effects of VPA, including its influence on tissue healing processes, especially in patients undergoing surgical interventions on the abdominal wall (FERREIRA, 2020).

Studies have shown that VPA acts as an inhibitor of histone deacetylases (HDACs), which can directly impact cell proliferation, fibroblast differentiation, and collagen deposition—key steps for efficient tissue repair. This epigenetic action can negatively interfere with the integrity and resistance of the surgical scar, generating specific concerns in patients who make continuous use of the drug and require surgeries such as herniorrhaphy or laparotomy (SOARES, LIMA, BARROS, 2021).

In surgical procedures involving the abdominal wall, proper tissue repair is essential to avoid complications such as dehiscence, incisional hernia formation, and infections. In this context, the presence of agents that can compromise the synthesis of extracellular matrix and the adequate remodeling of collagen fibers represents an important clinical challenge, with direct implications for surgical success and patient prognosis (ALMEIDA et al., 2019).

Thus, understanding the effects of valproic acid on the cellular and molecular mechanisms involved in abdominal tissue healing is essential to guide therapeutic approaches in neurological patients undergoing abdominal surgeries. Such research can provide important subsidies for preoperative medication adjustment and for the development of specific surgical and postoperative management strategies (SANTOS et al., 2022).

This study aimed to analyze the interference of valproic acid in abdominal wall healing, considering the possible effects on collagen synthesis, fibroblast proliferation and extracellular matrix integrity, and to discuss its clinical implications in abdominal surgeries.

MATERIALS AND METHODS

This is a literature review with a qualitative approach and exploratory character. The selection



of studies was carried out through the PubMed, SciELO, ScienceDirect and Scopus databases, with the choice of complete articles, published in peer-reviewed scientific journals, addressing the use of valproic acid in the context of tissue healing, especially in patients undergoing surgical procedures. The time frame of the research considered the period from 2018 to 2022, based on the oldest article (Costa et al., 2018) and the most recent (Santos et al., 2022; Alves et al., 2022; Moura et al., 2022).

- The following Health Sciences Descriptors were used:
- "Valproic Acid"
- "Wound Healing"
- "Collagen"
- "Tissue Regeneration"
- "Epigenetics"
- "Angiogenesis"
- "Oxidative Stress"
- "Surgery"
- "Epileptic Patients"
- The combinations of the descriptors were performed with the Boolean operators AND and OR. Key search strategies included:
- "Valproic Acid" AND "Wound Healing"
- "Valproic Acid" AND "Tissue Regeneration"
- "Valproic Acid" AND "Collagen"
- "Epigenetics" AND "Scarring"
- "Valproic Acid" AND "Oxidative Stress"
- "Healing" AND "Epileptic Patients"
- "Valproic Acid" AND "Surgery"



• Guiding Question:

What are the effects of valproic acid on tissue healing and regeneration processes in patients undergoing surgical procedures, considering epigenetic, inflammatory and structural mechanisms?

- Inclusion Criteria:
- Articles published between 2018 and 2022;
- Studies in Portuguese, English or Spanish;

- Publications that address the relationship between valproic acid and healing, tissue regeneration, collagen remodeling, or postoperative complications;

- Original articles, experimental studies, narrative or systematic reviews, and observational clinical studies.

• Exclusion Criteria:

- Articles that deal with the use of valproic acid in exclusively neurological or psychiatric contexts, unrelated to healing or surgery;

- Studies with animal models without human clinical correlation or direct applicability in surgery;

- Works not available in full text;
- Isolated case reports without experimental or pathophysiological basis.

THEORETICAL FOUNDATION

The tissue repair process of the abdominal wall depends on a series of coordinated cellular and molecular events, which include initial inflammation, fibroblast proliferation, angiogenesis, and collagen synthesis. Any factor that interferes with these steps can compromise the resistance of the scar and predispose to the formation of incisional hernias or dehiscence of the surgical wound.

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Valproic acid, by acting as an inhibitor of histone deacetylases (HDACs), can affect these mechanisms through changes in gene expression (MACHADO, 2020).

Experimental studies indicate that VPA can reduce fibroblast proliferation and deposition of type I collagen, which is essential for scar stability. This effect seems to be related to the epigenetic modulation promoted by the drug, which inhibits genes associated with the extracellular matrix and wound contraction, impairing the maturation of the surgical scar (RAMOS, TORRES, FERREIRA, 2021).

In addition, VPA has been associated with inhibition of angiogenesis in several biological models. The formation of new blood vessels is crucial for the supply of oxygen and nutrients to regenerating tissues. The inhibition of this process by valproic acid can delay or weaken healing, which becomes especially relevant in abdominal procedures with a higher risk of postoperative complications (COSTA et al., 2018).

It is important to consider that patients on continuous use of VPA, such as those with refractory epilepsy or psychiatric disorders, often cannot discontinue medication in the perioperative period. In these cases, it is essential that the surgeon is aware of the potential adverse effects of the drug on healing, in order to adopt preventive strategies, such as strengthening the abdominal wall with surgical meshes, intensive postoperative surveillance, and adjustments in the drug dose when possible (SILVA, LIMA, RIBEIRO, 2021).

Recent research has also explored the impact of VPA on the local inflammatory response. The balance between pro-inflammatory and anti-inflammatory mediators is essential for the normal progress of healing. VPA seems to interfere with this balance by inhibiting the activation of macrophages and the release of cytokines such as TGF- β and IL-6, which can impair the transition from the inflammatory to the proliferative phase of the healing process (ALVES et al., 2022).

The antiproliferative activity of valproic acid, although beneficial in oncological contexts, may have adverse effects in situations that require efficient cell regeneration, such as abdominal wall healing. The reduction in cell proliferation and myofibroblast migration, induced by epigenetic

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mechanisms, impairs the formation of granulation tissue and compromises the mechanical integrity of the surgical wound (TEIXEIRA, 2021). This interference represents a considerable risk in surgeries that require high resistance of the abdominal wall, such as exploratory laparotomy and hernial repairs.

Additionally, VPA interferes with collagen homeostasis, reducing not only its synthesis, but also affecting its structural organization and maturation. Studies have shown that valproic acid can alter the ratio between type I and type III collagen, unbalancing the extracellular matrix and resulting in scars that are less resistant and more susceptible to rupture (MOURA, ANDRADE, LEITE, 2022). This structural change can be decisive in patients undergoing abdominal surgeries under tension, increasing the rate of postoperative complications.

In addition, VPA can impair mitochondrial function and increase cellular oxidative stress, effects that are known to be deleterious to tissues in the process of repair. The increased production of reactive oxygen species can lead to the apoptosis of key cells in the healing process, such as fibroblasts and endothelial cells, delaying or making the normal progression of the healing phases unfeasible (LOPES et al., 2021). This effect is particularly relevant in immunocompromised patients or those with chronic comorbidities.

It should also be noted that the chronic use of VPA is associated with hepatic and hematological alterations, such as thrombocytopenia, which can indirectly affect the healing of surgical wounds. Reduced liver function compromises the production of plasma proteins important for inflammation and regeneration, while changes in coagulation can lead to inadequate clot formation, impairing the initial basis of healing (CUNHA et al., 2020).

CONCLUSION

The interference of valproic acid in tissue repair of the abdominal wall represents a relevant concern in the surgical context, especially in patients who use the medication continuously. Understanding the epigenetic, cellular, and biochemical mechanisms involved in the adverse effects of



this drug on healing allows us to identify risks and adopt safer preventive and therapeutic measures.

Considering that valproic acid can compromise fundamental processes such as fibroblast proliferation, collagen synthesis, angiogenesis, and control of the inflammatory response, it is essential that the surgeon be aware of the possible implications during the planning and conduct of abdominal interventions, such as laparotomy and hernial repairs. Careful preoperative evaluation and multidisciplinary follow-up can help minimize complications and promote better clinical outcomes.

Thus, this theme highlights the importance of an individualized approach in patients who use valproic acid and reinforces the need for further clinical and experimental studies that deepen the understanding of the interaction between neurological drugs and tissue regeneration processes in the surgical context.

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