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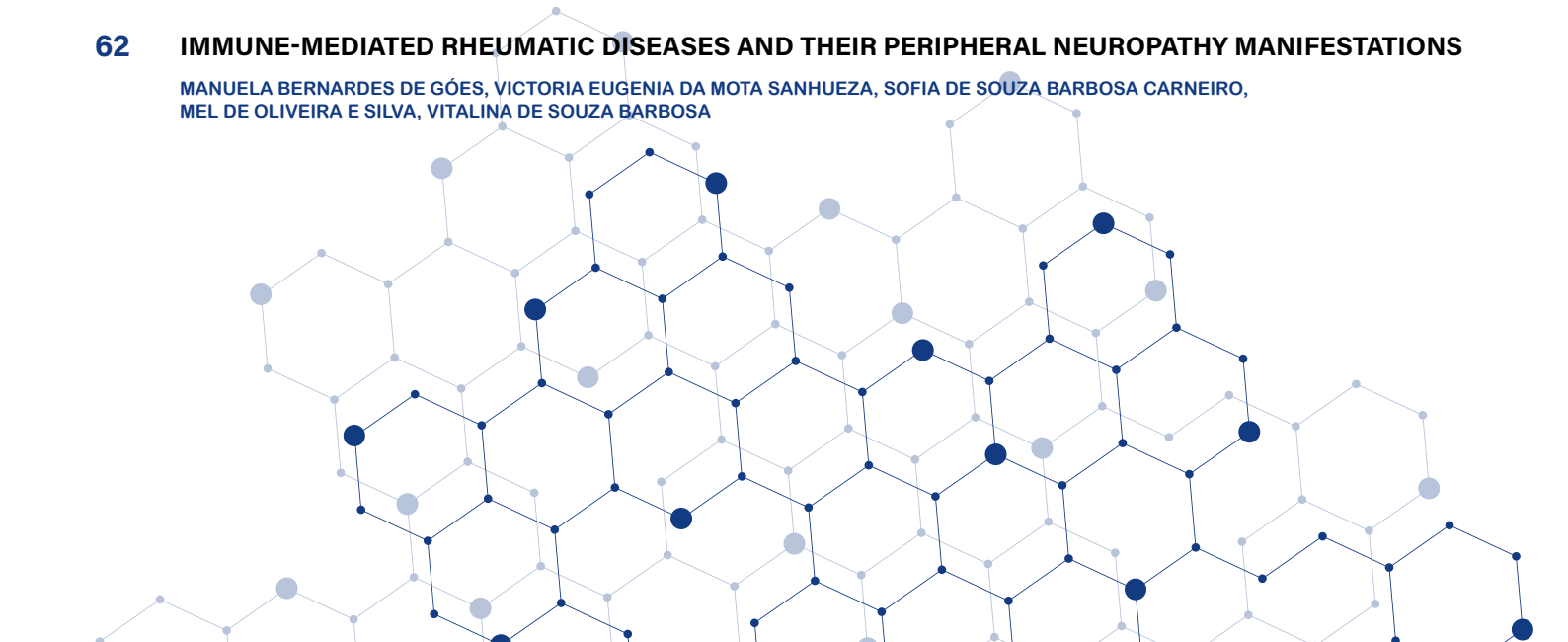

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SCIENTIFIC ARTICLE - CASE REPORT

ANESTHESIA IN CYTOREDUCTIVE SURGERY COMBINED WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY: A CASE REPORT

GABRIEL PEIXOTO NASCIMENTO[1], MATHEUS SILVA DE OLIVEIRA[1], ESTEVAM BORGES LOPES[1], GUSTAVO SIQUEIRA ELMIRO[1], GIULLIANO GARDENGHI [1,2]

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ABSTRACT

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has become an important approach in the treatment of several neoplasms with peritoneal dissemination. CRS is based on the excision of all macroscopic peritoneal metastatic lesions, while HIPEC is based on the elimination of circulating tumor cells and peritoneal micrometastases invisible to the naked eye. In this context, the clinical case presented involves a 41-year-old female patient who underwent CRS and HIPEC for the treatment of advanced gastric cancer with peritoneal carcinomatosis. Her anesthesia involved total intravenous general anesthesia associated with thoracic epidural, with fluid management guided by ultrasound parameters and management of adverse events, proving effective for the surgical and chemotherapy approach in question.

Keywords: Anesthesia general, Anesthesia epidural, Cytoreduction surgical procedures, Hyperthermic intraperitoneal chemotherapy, Peritoneal neoplasms.

INTRODUCTION

Cytoreductive surgery (CRS), with or without hyperthermic intraperitoneal chemotherapy (HIPEC), has become a cornerstone in the treatment of various neoplasms with peritoneal dissemination.[1] Currently, CRS/HIPEC represents a paradigm shift in the management of patients with peritoneal malignancies, improving prognosis in appendiceal, colorectal, ovarian tumors, and peritoneal mesothelioma.[2]

The fundamental principle of CRS lies in the complete excision of all macroscopic peritoneal metastatic lesions, often requiring extensive multivisceral resections within the abdominal cavity. This procedure aims to remove the primary tumor, tumor implants, and affected areas to reduce the tumor burden and enhance the efficacy of subsequent therapy.[3]

HIPEC, in turn, targets the eradication of circulating tumor cells and peritoneal micrometastases that are not visible to the naked eye. This therapeutic modality consists of the intraperitoneal administration of high-concentration, heated chemotherapeutic agents, immediately after surgical resection and

prior to reconstruction of the gastrointestinal tract.[4] The rationale for hyperthermia is based on the differential susceptibility of malignant cells to heat, resulting in selective destruction within the range of 41 to 43°C. Moreover, the microcirculation in many malignant tumors exhibits complete vascular stasis in response to hyperthermia. The synergy between heat and cytotoxic agents increases cytotoxicity by enhancing drug absorption through increased cell membrane permeability.[5]

The multimodal nature of these procedures for the treatment of abdominal neoplasms may induce significant tissue trauma, with subsequent inflammation and a risk of serious adverse effects reported in up to 51% of cases. Therefore, the implementation of specialized perioperative care is imperative.[6]

In this context, this article presents a case report of the anesthetic management of a patient who underwent CRS combined with HIPEC for the treatment of an intra-abdominal malignancy.

CASE REPORT

The patient is a 41-year-old female, weighing 60 kilograms and measuring 1.70 meters in height, with a positive family history of intestinal cancer and a personal diagnosis of advanced gastric cancer with peritoneal carcinomatosis. She has major depressive disorder and insomnia, treated with desvenlafaxine 100 mg/day and quetiapine 25 mg/day. She also has a history of cesarean section, abdominoplasty, exploratory laparoscopy, and port-a-cath implantation, with no previous anesthetic complications.

During the pre-anesthetic consultation, laboratory tests, electrocardiogram, and echocardiogram were normal. In addition, she was classified as low surgical risk according to cardiology assessment.

Upon arrival in the operating room, the patient underwent monitoring with invasive blood pressure, central venous pressure (CVP), cardioscopy, thermometry, capnography, and depth of anesthesia monitoring. Sedation was initiated with 5 mg of midazolam, followed by epidural puncture at the T8–T9 level using an 18G Tuohy needle, with insertion of an 18G epidural catheter, advanced 5 cm beyond the puncture site.

Subsequently, total intravenous general anesthesia (TIVA) was induced with propofol 150 mg, sufentanil 20 mcg, and rocuronium 50 mg. Direct laryngoscopy (Cormack-Lehane grade 1) was performed, followed by orotracheal intubation with a 7.5 mm tube. Anesthesia was maintained with target-controlled infusion (TCI) of propofol, and an epidural infusion containing ropivacaine 150 mg, fentanyl 100 mcg, and clonidine 150 mcg.

Adjuvant medications included: cefazolin 3 g, metronidazole 1000 mg, dexamethasone 10 mg, dipyrone 4 g, ondansetron 8 mg, parecoxib 40 mg, pantoprazole 40 mg, vitamin C 2 g, and vitamin B complex.

Intraoperatively, peritoneal tumor implants smaller than 5 mm were observed in the cul-de-sac, pelvic-vesical peritoneum, and pancreatic capsule, along with neoplastic involvement of the gastric antrum and body. The surgical procedures performed included total hysterectomy with adnexectomy, rectosigmoidectomy, total gastrectomy with lymphadenectomy, and pelvic peritonectomy.

Following cytoreductive surgery, HIPEC was performed using 5% dextrose solution and oxaliplatin, infused at 42°C for 60 minutes. At the end of the procedure, the HIPEC solution was drained after reopening the abdominal cavity and rinsing with normal saline.

During surgery, fluid resuscitation with crystalloids was guided by fluid responsiveness assessment. Due to the ease of anatomical access without interfering with the surgical field, carotid peak velocity variation was evaluated using pulsed Doppler ultrasound. This assessment was performed after each 1000 ml infusion of warmed lactated Ringer's solution, totaling 7000 ml administered.

During the HIPEC phase, the patient developed hyperglycemia, with wide glycemic variability, requiring continuous intravenous insulin infusion. She also experienced an episode of hypotension, which required low-dose norepinephrine support.

At the end of the procedure, the patient was extubated in the operating room and transferred to the intensive care unit (ICU) with a mean arterial pressure (MAP) of 80 mmHg, CVP of 3 mmHg, and norepinephrine infusion at 0.08 mcg/kg/min. Bedside lung ultrasound (POCUS) showed no signs of congestion, with inferior vena cava diameter less than 2 cm and capillary refill time of 2 seconds (Figure 1).

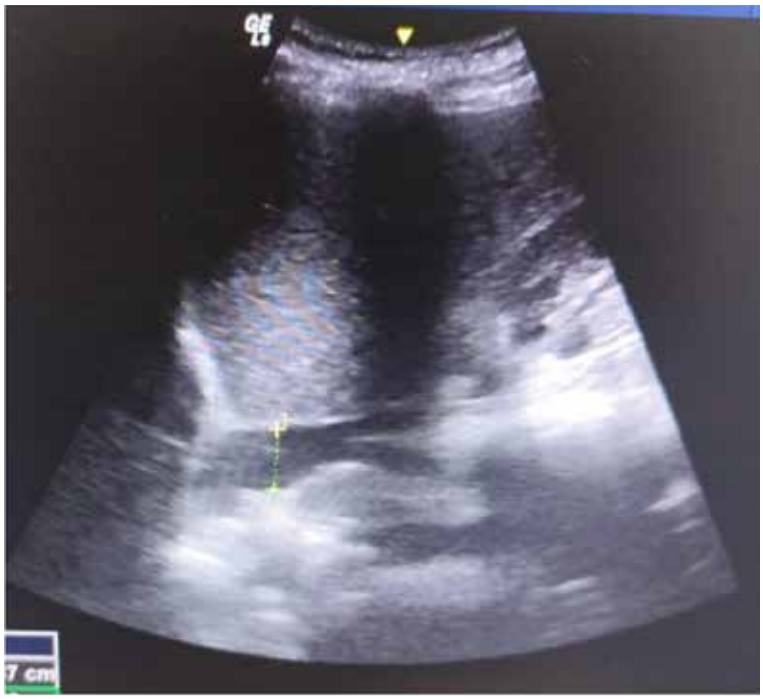

Figure 1. Inferior vena cava ultrasound of the patient in the case, showing a diameter of 1.87 cm

During the first 48 hours of the postoperative period, the patient received an infusion of 0.2% ropivacaine and fentanyl via epidural catheter while in the ICU. During daily evaluations by the anesthesiology team, the patient showed no motor block and reported only palpation-induced pain with an intensity of 3/10 during the first 24 hours, with no further complaints thereafter.

DISCUSSION

Peritoneal carcinomatosis (PC), characterized by the dissemination and implantation of neoplastic cells within the peritoneal cavity, is a common complication of primary malignancies originating in intraperitoneal organs. Disease progression involves invasion of the serosal surface of the primary organ, dissemination of tumor cells, followed by cellular proliferation and neovascularization, resulting in the formation of tumor nodules. This condition is associated with high morbidity and mortality and is observed in 75% of ovarian cancers, 5–10% of colorectal tumors, and 14% of gastric cancers, particularly those arising from gastrointestinal and gynecological tumors.[7]

The implementation of Enhanced Recovery After Surgery (ERAS) protocols is essential in the perioperative management of patients undergoing major procedures such as CRS and HIPEC. These protocols aim to modulate the postoperative metabolic and inflammatory response, optimize care, and consequently reduce complications, length of hospital stay, and costs. Strict adherence to ERAS guidelines has been shown to positively impact clinical outcomes.[8]

Preoperative assessment is a critical component of ERAS protocols for major oncological and abdominal surgeries. Its primary goal is to evaluate the patient's clinical condition, determine the ability to tolerate anesthesia and surgery, mitigate perioperative risks, and prepare the patient for surgery.[9] Cardiovascular evaluation, in particular, is of paramount importance. Patients with reduced cardiac reserve, a history of heart failure, or chemotherapy-induced cardiotoxicity may require additional tests such as echocardiography or stress testing for optimal preoperative planning. In the present case, the patient had normal cardiac function on echocardiography.[10]

Regarding the choice of anesthetic technique, although no approach has demonstrated clear superiority for CRS ± HIPEC, evidence suggests that total intravenous anesthesia (TIVA) may be associated with better long-term outcomes in oncologic surgery. Additionally, TIVA has been shown to reduce the incidence of postoperative nausea and vomiting (PONV) in high-risk groups, particularly in the early postoperative period, compared to inhalational anesthesia.[11] Epidural analgesia, in turn, provides excellent pain control in major laparotomies and may reduce pulmonary complications. Prolonged thoracic epidural analgesia (beyond 72 hours) has been investigated for its potential contribution to disease-free survival and overall survival.[12]

Intraoperative glycemic control is an essential measure to minimize postoperative morbidity and mortality in patients undergoing CRS and HIPEC. Factors related to CRS (surgical stress, fasting, fluid administration) and to HIPEC (hyperthermia, chemotherapy, intraperitoneal carrier solutions) contribute to glycemic variability, justifying rigorous monitoring and management.[13]

With regard to fluid replacement, despite capillary leak and significant fluid, blood, and protein loss observed in patients undergoing CRS and HIPEC, liberal administration of crystalloids may exacerbate interstitial edema. This, in turn, can negatively affect vital organs and intestinal anastomoses, increasing the risk of fistula formation. Therefore, crystalloid infusion should be guided by hemodynamic parameters and individualized for each patient.[14]

Early extubation is encouraged in ERAS protocols, as it facilitates early ambulation, reduces the need for prolonged sedation, and contributes to the rapid return of intestinal function and overall recovery. The presence of an epidural catheter and the infusion of local anesthetics reduce the need for opioids during the intraoperative and immediate postoperative phases, supporting early extubation.[10]

For postoperative analgesia, thoracic epidural analgesia (TEA) is considered the gold standard following extensive laparotomies. It helps restore intestinal function, supports anastomotic integrity, and reduces pulmonary complications. The combination of low concentrations of local anesthetics with a short-acting opioid appears to be the most effective strategy to optimize analgesia while minimizing the risk of motor block and sympathetic block–induced hypotension.[15]

CONCLUSION

CRS combined with HIPEC produces physiological and potentially pathological changes with important implications for anesthetic care, making it challenging and requiring special attention. Evidence-based protocols and recommendations, such as ERAS, are timely and represent a crucial advancement in

the evolution of perioperative management for patients affected by malignant peritoneal surface neoplasms.

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SCIENTIFIC ARTICLE - CASE REPORT

BALANCED GENERAL ANESTHESIA FOR STEM CELL MEMBRANE INSERTION IN A BRONCHOPLEURAL FISTULA: A CASE REPORT

FELIPE MENDES FARIA[1], LARISSA MANZAN DE ALCANTARA BORGES[1], MATHEUS SILVA DE OLIVEIRA[1], PLINIO ALMEIDA PINHEIRO DE BELEM[1], GUSTAVO SIQUEIRA ELMIRO[1], GIULLIANO GARDENGHI[1,2]

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ABSTRACT

Bronchopleural fistula is a multifactorial pathological condition that remains difficult to resolve and is associated with high morbidity. With advances in medical science, there has been a growing number of studies on the use of stem cell therapy in the treatment of diseases that previously had few alternatives to achieve a cure. Mesenchymal stem cells have emerged as a promising therapeutic component, primarily due to their intrinsic ability to secrete pro-angiogenic cytokines and modulate the tissue microenvironment, thereby directing recruited cells toward effective wound healing. This case report describes an elderly female patient with multiple comorbidities who underwent closure of a bronchial fistula using a platelet-rich fibrin and leukocyte membrane (PRFL), obtained via centrifugation of mesenchymal cells through a one-step technique during the surgical procedure. The intervention was performed under balanced general anesthesia and required heightened vigilance due to several episodes of apnea needed for membrane placement. The procedure was completed successfully, with favorable outcomes observed in all phases.

Keywords: Bronchial fistula, Stem cells, Thoracic surgery; Wound healing, Lung.

INTRODUCTION

Bronchopleural fistula (BPF) is a serious and life-threatening complication in pulmonary medicine and intensive care, characterized by high morbidity and mortality rates. This pathological communication establishes a direct tract between the bronchial tree and the pleural space, and its etiology is multifactorial. Among the most prevalent causal factors are iatrogenic injuries related to invasive thoracic procedures such as lung biopsy, pleural drainage, and thoracentesis, as well as distinct pathologies such as pneumonia complicated by empyema, pulmonary neoplasms, and blunt or penetrating chest trauma.[1] However, the incidence of BPF is most frequently observed in the postoperative context of pulmonary resections, typically as a consequence of inadequate bronchial stump healing.[1]

In the field of regenerative medicine, mesenchymal stem cells (MSCs) have emerged as a promising therapeutic agent. This potential is primarily attributed to their intrinsic ability to secrete pro-angiogenic cytokines and to modulate the tissue microenvironment, directing recruited cells toward an effective resolution of wound healing processes.[2] Furthermore, MSCs exhibit remarkable immunomodulatory and anti-inflammatory properties, which are crucial attributes for mitigating tissue damage and facilitating repair in various experimental injury models.[2]

The application of cell-based therapies, particularly those involving MSCs, has shown potential to modulate the local inflammatory response and promote angiogenesis. These processes are critical for tissue repair in complex scenarios such as BPF.[2] The ability of MSCs to interact with immune system cells—modulating their phenotype and the secretion of mediators—suggests a relevant role in orchestrating the cellular events necessary for fistula closure and the restoration of tissue integrity.[3]

The objective of the present study is to evaluate the therapeutic potential of applying products derived from autologous MSCs and growth factors in the resolution of a persistent BPF.

CASE REPORT

This A 72-year-old female patient presented with a complex medical history of comorbidities, including rheumatoid arthritis, systemic arterial hypertension, type 2 diabetes mellitus, hypothyroidism, and lung carcinoma. Her regular medications included levothyroxine, pantoprazole, multivitamin, metoprolol, ferrous sulfate, acetylsalicylic acid, extended-release metformin, methotrexate, alendronate, and zolpidem. Her surgical history included hysterectomy, cholecystectomy, and left upper lobectomy for adenocarcinoma.

In the surgical setting, the anesthesiology team instituted standard monitoring, including noninvasive blood pressure, pulse oximetry, electrocardiography, body temperature, capnography, and urinary output measurement. After obtaining peripheral venous access with an 18G catheter, preoxygenation was performed with a fraction of inspired oxygen (FiO_2) of 100% for 5 minutes. Intravenous anesthesia induction consisted of 2% lidocaine (without vasopressor), 20 mcg of sufentanil, 30 mg of rocuronium, and 120 mg of propofol. Orotracheal intubation was performed using a 7.0 mm cuffed tube under atraumatic direct laryngoscopy, with verification of correct placement and protection of the eyes and bony prominences. Balanced general anesthesia was maintained with controlled mechanical ventilation using 2% sevoflurane and continuous infusion of remifentanil. Adjuvant medications administered included 10 mg of dexamethasone, 2 g of dipyrone, 8 mg of ondansetron, and 10 mg of aramine.

The surgical procedure was divided into four distinct phases. Initially, the plastic surgery team performed liposuction of the pubic region and abdominal flanks, with the patient in the supine position, to collect mesenchymal cells (stem cells) using the one-step technique. Subsequently, the lipoaspirated material was subjected to centrifugation to isolate the mesenchymal cells (Figure 1). Concurrently, peripheral blood was drawn from the patient to prepare an Injectable Platelet-Rich Fibrin (i-PRF) membrane and a Platelet- and Leukocyte-Rich Fibrin (PRF-L) membrane (Figure 2).

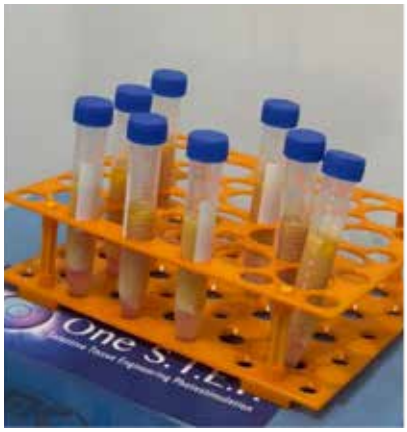

Figure 1: Material subjected to centrifugation for mesenchymal cell separation.

Figure 2: Preparation of i-PRF (Injectable Platelet-Rich Fibrin) and PRF-L (Platelet- and Leukocyte-Rich Fibrin) membranes

In the third phase, the thoracic surgery team performed rigid bronchoscopy, identifying the BPF (Figure 3). PRF-i and ADSVF (autologous adipose-derived stromal vascular fraction) were then implanted in two layers, along with PRF-L on the bronchial stump fistula (Figure 4). During this critical phase, the patient experienced episodes of apnea lasting several minutes due to disconnection from mechanical ventilation in order to optimize surgical material placement. At the end of this stage, a control flexible bronchoscopy revealed the final appearance of the bronchial stump.

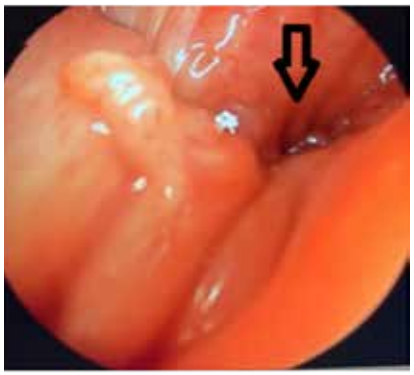

Figure 3: Bronchopleural fistula.

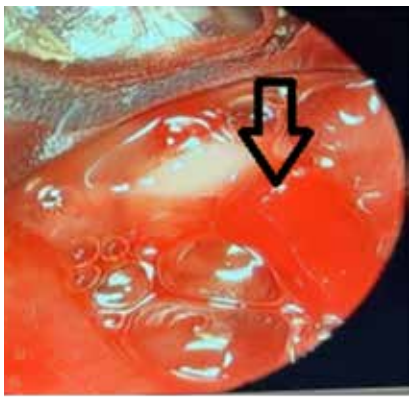

Figure 4: PRF-L membrane (Platelet- and Leukocyte-Rich Fibrin) inserted into bronchopleural fistula.

Subsequently, during thoracic surgery, a thoracostomy was performed at the level of the left fourth intercostal space, followed by the insertion of a small-caliber chest drain. At the end of the procedure, neuromuscular blockade reversal was achieved with the administration of 200 mg of sugammadex. The patient was then extubated and transferred to the post-anesthesia care unit, where she remained for approximately 60 minutes. After reaching the maximum score (10) on the Aldrete and Kroulik scale, she was transferred to a hospital room.

Two months after the initial surgical procedure, a follow-up bronchoscopy was performed, confirming complete closure of the bronchopleural fistula (BPF).

DISCUSSION

BPF consists of a pathological communication between the bronchus and the pleural space, with diverse etiologies. Notable causes include complications from surgical procedures such as lung biopsy, thoracic drainage, and thoracentesis, as well as clinical conditions such as pneumonia/empyema, pulmonary neoplasms, and blunt or penetrating chest trauma. However, BPF most frequently presents as a late complication of pulmonary surgeries, secondary to failed healing of the bronchial stump. This inadequate healing may be attributed to factors such as an initially

suboptimal surgical closure, insufficient blood supply, local infection, or the presence of residual malignant tumor at the bronchial stump.[1]

Clinically, BPF may present with cough, dyspnea, fever, and serosanguinous or purulent expectoration. Radiographically, changes in the air-fluid pattern in the chest may raise diagnostic suspicion. In cases of large fistulas, acute respiratory failure may occur due to aspiration into the contralateral lung or the development of tension pneumothorax.[1]

MSCs play a crucial role in modulating immune responses and suppressing inflammation. These cells exhibit significant anti-inflammatory properties, which are essential for minimizing tissue damage and promoting repair in various injury models. The involvement of MSCs in tissue regeneration is intrinsically linked to their ability to modulate inflammatory processes, including the efficient removal of cellular debris and activation of the MSCs themselves. However, chronic inflammation may impair the functionality of these cells by altering the cellular microenvironment or directly interfering with their differentiation mechanisms.[2]

MSCs are widely recognized for their dual role in promoting angiogenesis and vasculogenesis, while simultaneously exerting immunosuppressive and anti-apoptotic effects. Their ability to modulate the local immune response by altering the inflammatory phenotype of macrophages is particularly relevant in the context of BPF.[2]

The healing process is characterized by dynamic changes in macrophage subsets during the inflammatory phase, which differ from the cellular profiles observed in non-inflammatory conditions. A key component in the resolution of inflammation is the phenotypic transition of macrophages from a pro-inflammatory state to an anti-inflammatory profile, which not only suppresses inflammation but also promotes tissue regeneration. Additionally, macrophages play an essential role in the activation of stem cells in various tissues, significantly contributing to regenerative processes.[2,4]

A synergistic interaction is observed between macrophages and stem cells, similar to that described between macrophages and hematopoietic stem cells in the bone marrow, or with osteoblasts on bone surfaces. Previous evidence has shown that bone marrow–derived MSCs are capable of inducing macrophage polarization toward the M2 phenotype, an effect largely mediated by inhibition of the NF-κB signaling pathway.[2]

The treatment and resolution of the fistula require complex coordination among coagulation, inflammation, and angiogenesis processes. Inflammation, as an initial and essential response, plays a decisive role in the proper progression of healing. The duration and chronic nature of the inflammatory response directly influence the speed and effectiveness of healing, with persistent inflammation often associated with the development of chronic, hard-to-heal wounds, ultimately compromising the entire regenerative process.[2] There is evidence that stem cells may represent a new therapeutic option for severe pulmonary diseases.[5]

CONCLUSION

Given the relevance of the topic addressed, the importance of stem cells in the context of contemporary medicine is underscored. The PRF-L membrane represents a promising therapeutic option for the closure of BPF. It is evident that continued research on this subject will significantly expand the range of management possibilities for patients with this condition.

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SCIENTIFIC ARTICLE - CASE REPORT

POINT-OF-CARE GASTRIC ULTRASOUND ASSESSMENT GUIDING SAFE ANESTHESIA IN A PATIENT ON PROLONGED ORAL SEMAGLUTIDE USE: A CASE REPORT

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ABSTRACT

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs), such as semaglutide, delay gastric emptying and may increase the risk of pulmonary aspiration during general anesthesia. We report the application of point-of-care gastric ultrasound (POCUS-G) to stratify this risk in a chronic user of oral semaglutide. Case report: A 40-year-old woman, ASA II, with persistent post-gestational diabetes mellitus, on oral semaglutide 7 mg/day for 12 months (discontinuation advised 15 days prior to surgery). A 12-hour fasting period was confirmed. POCUS-G revealed an antral cross-sectional area of 5.81 cm^2 in the supine position and 4.94 cm^2 in the right lateral decubitus position; estimated gastric volume was 49 mL (0.72 mL/kg), below the high-risk threshold of 1.5 mL/kg. General anesthesia with a modified rapid sequence induction was performed uneventfully. POCUS-G enabled safe anesthetic management and avoided surgical cancellation. This technique supports individualized decision-making in patients using GLP-1 RAs.

Keywords: Glucagon-like peptide-1 receptor agonists, Ultrasonography, Gastric emptying, Respiratory aspiration, Anesthesia.

INTRODUCTION

Bronchopleural Pulmonary aspiration of gastric contents remains one of the most feared complications of general anesthesia. It occurs in approximately 1 in every 2,000–3,000 procedures and may evolve with high mortality, particularly if it results in chemical pneumonitis or ARDS.[1]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), especially semaglutide, have transformed the management of type 2 diabetes and obesity: in addition to improving glycemic control and reducing cardiovascular events, they delay gastric emptying by increasing pyloric tone and modulating vagal activity.[2] Since their introduction in 2017 (weekly subcutaneous) and 2019 (oral formulation), semaglutide has maintained this profile owing to its high receptor affinity and long plasma half-life. Studies have shown that this delayed emptying may persist even after prolonged fasting, which explains recent

reports of intraoperative aspiration events in patients using the drug.[3]

In this context, gastric point-of-care ultrasound (POCUS-G) has gained importance as a rapid screening tool for residual gastric volume and has been incorporated into guidelines that also recommend withholding GLP-1 RAs in symptomatic patients or those with recent dose escalation.[4] The present case report aims to describe the application of POCUS-G in the preoperative evaluation of a patient on chronic semaglutide therapy, highlighting its usefulness in stratifying aspiration risk and guiding safe anesthetic management.

CASE REPORT

A 40-year-old female patient, weighing 68 kg and measuring 1.65 m (BMI 24.98 kg/m²), classified as ASA II, with type 2 diabetes mellitus treated for twelve months with oral semaglutide 7 mg, which had been discontinued 18 days prior to undergoing abdominoplasty combined with medium-volume liposuction. Her history also included a small anterior cerebral aneurysm without clinical repercussions, in addition to chronic use of pitavastatin 2 mg and topical minoxidil. She denied allergies, smoking, or illicit drug use and had an estimated functional capacity between four and seven METs. A fasting period of twelve hours for solids and liquids was observed.

In the operating room, gastric POCUS was performed, showing an antral cross-sectional area of 5.81 cm² in the supine position and 4.94 cm² in the right lateral decubitus (Figure 1), corresponding to an estimated residual gastric volume of 49 mL (0.72 mL·kg-¹), below the risk threshold for aspiration, allowing the procedure to continue with a modified rapid-sequence induction. Multiparametric monitoring was established, including noninvasive blood pressure, ECG, SpO_2, Conox®, esophageal temperature, urine output, and capnography after intubation, along with intravenous access via the left upper limb using a 20 G catheter connected to two infusors.

Subsequently, during thoracic surgery, a thoracostomy was performed at the level of the left fourth intercostal space, followed by the insertion of a small-caliber chest drain. At the end of the procedure, neuromuscular blockade reversal was achieved with the administration of 200 mg of sugammadex. The patient was then extubated and transferred to the post-anesthesia care unit, where she remained for approximately 60 minutes. After reaching the maximum score (10) on the Aldrete and Kroulik scale, she was transferred to a hospital room.

Two months after the initial surgical procedure, a follow-up bronchoscopy was performed, confirming complete closure of the bronchopleural fistula (BPF).

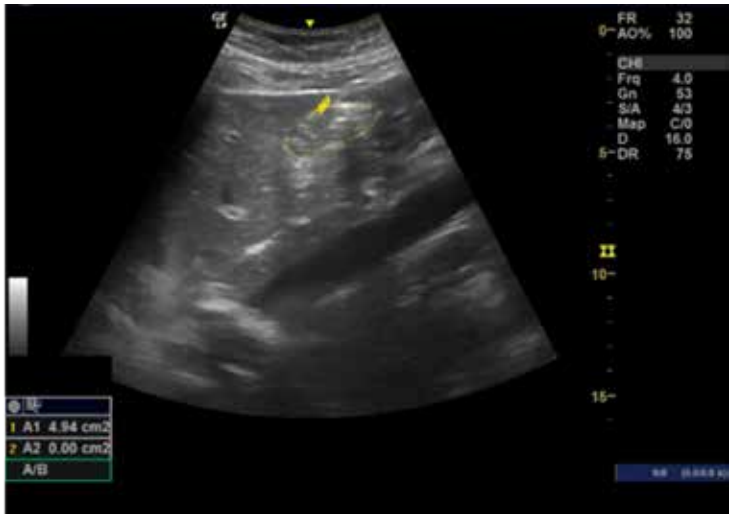

Figure 1 . Ultrasonographic image of the gastric antrum showing an area of 4.94 cm² with the patient in the right lateral decubitus position.

After premedication with midazolam 5 mg, a thoracic epidural block at T6–T7 was attempted using an 18 G Tuohy needle with the Dogliotti technique; however, blood reflux was observed after the injection of 3 mL of lidocaine, leading to abortion of the procedure. This was followed by preoxygenation with 100% oxygen for three minutes and intravenous induction with sufentanil 20 µg, target-controlled infusion of propofol (Ce 4 µg·mL-¹), and cisatracurium 0.15 mg·kg-¹. Direct laryngoscopy revealed a Cormack-Lehane grade I view, allowing tracheal intubation with a cuffed 7.5 mm endotracheal tube. Ventilation was set to volume-controlled mode with a tidal volume of 400 mL, respiratory rate of 12 bpm, PEEP of 5 cmH_2O, and FiO_2 of 0.5.

Anesthesia was maintained with multimodal TIVA: propofol TCI (Ce 3–4 µg·mL-¹, approximate infusion 9 mL·h-¹), dexmedetomidine at 0.5 µg·kg-¹·h-¹, ketamine at 0.3 mg·kg-¹·h-¹, additional sufentanil to a total of 30 µg, and an extra dose of cisatracurium 10 mg. As prophylaxis and adjuvants, the following were administered: cefazolin 2 g before incision (repeated with 1 g after three hours), dexamethasone 10 mg, dipyrone 4 g (fractionated), ondansetron 8 mg, parecoxib 40 mg, pantoprazole 40 mg, methadone 10 mg, haloperidol 2 mg, tranexamic acid 1 g, and boluses of aramina as required. Eye protection and careful padding of plexuses, joints, and bony prominences were applied. Fluid management included 250 mL of 0.9% saline solution and 3 L of Ringer's lactate.

The surgical procedure lasted approximately 95 minutes, proceeding with hemodynamic stability, blood loss below 150 mL, and adequate urine output. At the end, the patient was extubated under deep anesthesia with Conox® around 60, maintained on oxygen at 5 L·min-¹ via facemask, and transferred to the post-anesthesia care unit, where she achieved an Aldrete and Kroulic score of 10 within fifteen minutes, reporting pain at 2/10 and no nausea. After twelve hours of observation, she tolerated oral intake, maintained target blood glucose levels, and was discharged without complications.

This case demonstrates that, even after prolonged discontinuation of semaglutide, delayed gastric emptying remains uncertain, with gastric ultrasound serving as a valuable tool to confirm an empty stomach and to allow a safe modified rapid-sequence induction. Although the epidural

attempt was unsuccessful, multimodal analgesia with dexmedetomidine, ketamine, and methadone provided effective postoperative comfort, enabling early discharge following medium-complexity plastic surgery.

DISCUSSION

BPF Since Mendelson's classic description, it has been established that the severity of pulmonary aspiration depends on two central factors: gastric pH < 2.5 and aspirated volume > 0.3 mL·kg-¹ (≈ 25 mL in adults), parameters that amplify the chemical–inflammatory alveolar injury.[4] Acidic contents precipitate epithelial apoptosis, generate reactive oxygen species, and activate NF-κB, a cascade that may culminate in acute respiratory distress syndrome (ARDS) if the proinflammatory response is not interrupted[5]. Protective ventilation safeguards the remaining parenchyma, but mortality in contemporary series still exceeds 40%.[6]

GLP-1 receptor agonists, particularly semaglutide, exacerbate this risk by delaying gastric emptying. The drug activates vagal afferents in the dorsal medulla and, through central GABA release, reduces sympathetic drive while increasing pyloric tone; in parallel, it inhibits interstitial cells of Cajal, reducing slow-wave activity and antral peristalsis[7]. Electrogastrography after 12 weeks of use demonstrates bradygastria and increased frequency of dysrhythmias.[8] Pharmacokinetically, semaglutide has an oral bioavailability of only 0.4–1%, but its prolonged half-life (≈ 168 h), sustained by strong albumin binding, maintains therapeutic concentrations across several dosing intervals after discontinuation. This explains reports of a still-full stomach 7–10 days after the last dose and supports the recommendation to withhold the drug for at least one week before elective surgery[9]. Although partial tachyphylaxis of delayed gastric emptying occurs after 20 weeks, clinically relevant slowing persists, particularly in obese patients or those with other causes of gastroparesis[10]. Gastric emptying scintigraphy shows that the time required for 50% of ingested radioactive material to leave the stomach, known as gastric emptying half-time (T_{50}), remains prolonged in more than 30% of individuals four weeks after discontinuation, suggesting remodeling of myoenteric motor neurons or adaptive resistance to motilin[11]. Gastric POCUS has emerged as a quantification tool: a meta-analysis of 1,200 patients demonstrated 95% sensitivity and 90% specificity for identifying high-risk stomachs (≥ 1.5 mL·kg-¹ or the presence of solids)[12]. However, BMI > 40 kg·m-², late pregnancy, and bariatric surgery impair acoustic windows, requiring experienced operators. Novices need 24–33 examinations to achieve 90% agreement with experts, and the average acquisition time stabilizes at < 60 s after 40 scans[13]. Although scintigraphy remains the gold standard for T_{50} (≈ 105 min for half the meal), its cost, radiation exposure, and need for prolonged fasting limit routine use; agreement between gastric POCUS and scintigraphy is excellent for liquids, but diverges for fiber-rich solids.[14]

Based on these data, perioperative management can follow a pragmatic algorithm: discontinue GLP-1 RAs seven days before elective surgery in patients on weekly regimens or after recent dose escalation, according to ASA guidelines[15] and multisociety consensus[16]; perform gastric POCUS and proceed if the estimated volume is < 1.5 mL·kg-¹, given its high discriminatory power[12]; in cases of elevated volume or solids, consider postponing the procedure, inserting a nasogastric tube before induction, or administering erythromycin 3 mg·kg-¹ IV as a prokinetic agent[17]; conduct rapid-sequence induction with rocuronium 1.2 mg·kg-¹ while keeping sugammadex available[18]; prefer a definitive airway, although second-generation laryngeal masks are acceptable for short surgeries under endoscopic supervision, as they do not increase aspiration rates compared with endotracheal tubes (RR 0.96)[19]; and restart GLP-

1 RA therapy only after resumption of diet and ambulation, to avoid late hypoglycemia.[20]

Significant gaps remain, including defining the kinetics of return to baseline T_{50} by serial scintigraphy in different metabolic profiles; developing predictive models that combine clinical variables, gastric POCUS, and pharmacokinetics through machine learning to anticipate volumes greater than 0.8 mL·kg-1 with an AUC above 0.9; clarifying interactions between semaglutide, opioids, anticholinergics, and NK1 receptor antagonists; conducting randomized trials comparing treatment continuation versus discontinuation with respect to glycemic control, respiratory complications, and length of hospital stay; and validating serum biomarkers such as motilin, peptide YY, and GLP-2 as rapid indicators of residual gastric emptying.[21]

CONCLUSION

The risk of pulmonary aspiration in patients using semaglutide arises from complex neurohormonal mechanisms that prolong gastric emptying time even after discontinuation of the drug. The combination of objective stratification through gastric POCUS, selective discontinuation of the medication, prokinetic measures, and advanced airway protection techniques represents the most robust strategy currently available, but significant gaps remain and should guide future investigations.

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SCIENTIFIC ARTICLE - CASE REPORT

ETHNIC SUICIDE: AN AVOIDABLE PHENOMENON AMONG INDIGENOUS CHILDREN OF THE BRAZILIAN AMAZON

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ABSTRACT

The indigenous population is particularly vulnerable to psychiatric disorders and suicide, as recorded worldwide among various ethnic groups and ancestral peoples. We present a case report to illustrate the psychopathological phenomenon of psychotic depression with suicidal behavior in a Karajá indigenous child, documenting the possibility of successful medical intervention to prevent suicide, despite the obstacles posed by the Brazilian government that hinders the treatment of this vulnerable and at-risk population, clearly revealing the neglect of psychiatric care for Brazilian indigenous children. Indigenous children seem especially vulnerable to psychiatric disorders and suicide, even though they are culturally more isolated than adults and have had less exposure to non-indigenous culture. This serious situation and public health problem among indigenous people are still interpreted in a romanticized, inappropriate manner, with a strong sociological bias, to the detriment of modern approaches to mental health based on Neurosciences. Denying children access to treatment, regardless of or because of their ethnicity, especially when their lives are at risk, may constitute a crime according to the standards regulating humanitarian treatment that our civilization has achieved.

Keywords: Indigenous, Amazon, Mental health, Psychiatric disorders, Suicide, Karajá Ethnicity.

INTRODUCTION

The native indigenous communities of Brazilian territory total approximately 817,000 people, distributed across 305 ethnic groups.[1] The Karajá people represent one of the most traditional and preserved ancestral communities, with a rich culture of collectors, fishermen, and hunters, living in a manner very similar to our ancestors from 10,000 years ago, in a pre-agriculture period. The Karajá people traditionally survive through fishing, hunting, and gathering fruits and roots from the Cerrado.

Art and ceramics are important cultural expressions for this ethnic group. They are known for their skill in creating decorative ceramics, which are used in rituals and ceremonies. The pieces are adorned with colored graphic designs (geometric drawings) and represent animals and human figures.[2,3]

This ethnic group belongs to the Macro-Jê language family and uses the native language Iny rybè, in addition to Portuguese. They have a social division in which men play roles such as hunting, fishing, defending the territory, political leadership, and building the villages. Women are responsible for the care and upbringing of children, performing domestic tasks, artistic work such as painting for ritual ceremonies, and making ceramic dolls, as well as preparing food for festivals.[2]

The Karajá people primarily inhabit the Araguaia River basin, occupying lands in the states of Mato Grosso, Tocantins, and Goiás, in a transition area from the Cerrado to the Legal Amazon[2] (figura 1). (Figure 1). The ethnic group has a population of 4,326 people. Each village establishes a specific territory, demarcating internal cultural spaces for their ritual practices, fishing, and hunting.[1]

The indigenous population is particularly vulnerable to psychiatric disorders and suicide, as recorded worldwide among various indigenous peoples and ancestral ethnic groups. The study and approach to psychiatric disorders and suicide among Brazilian indigenous people have been neglected for centuries and continue to be so to this day, with very little scientific literature on this topic and the absence of clear and effective public health policies. Since the 1990s, with the epidemic of alcohol and drug use and the announcement of alarming suicide rates among indigenous people, academic and media interest in this and other phenomena related to indigenous mental health has emerged.[4,5,6]

We present a case report to illustrate the psychopathological phenomenon of psychotic depression with suicidal behavior in a Karajá indigenous child, documenting the possibility of successful medical intervention to prevent suicide, despite the obstacles posed by the Brazilian government that hinders the treatment of this vulnerable and at-risk population, clearly revealing the neglect of psychiatric care for Brazilian indigenous children.

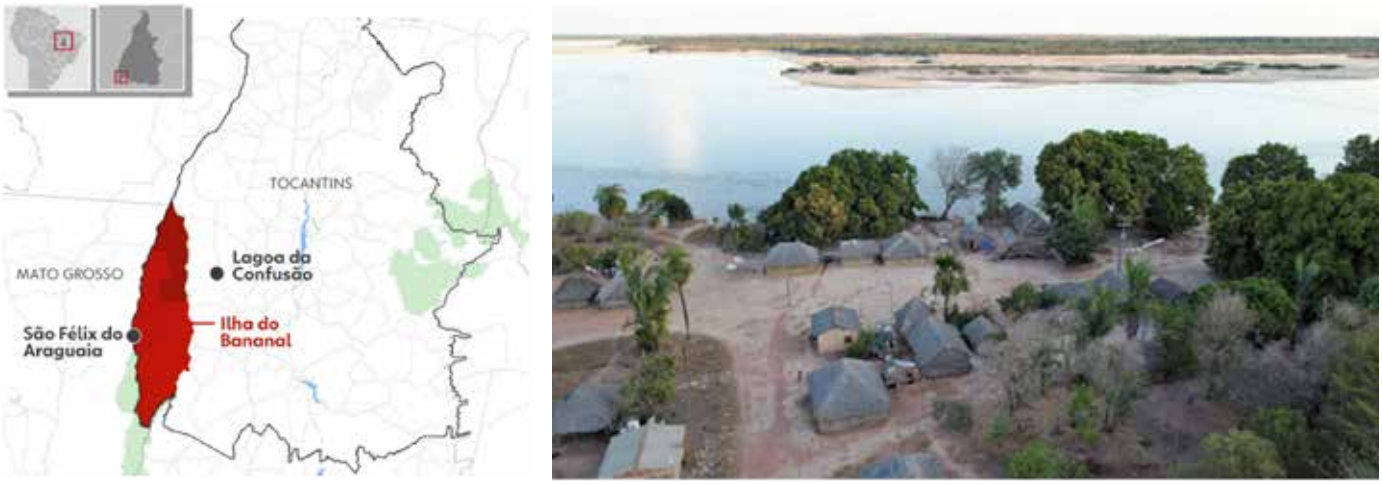

Figure 1 – Geographic location of Bananal Island (above) and Karajá village (right side).

CLINICAL CASE

Ibòò marãdu (fictitious name), 10 years old, male, indigenous child from the Karajá ethnic group, lives in a relatively isolated village on the largest river island in the world: Bananal Island, on the banks of the Araguaia River (Figure 1). Ibòò marãdu has very little contact with non-indigenous people, living with his community of nearly 3,500 individuals. Ibòò marãdu began a two-month history of a typically depressive syndrome (depressed mood, easy crying, irritability, anxiety, distress, loss of appetite and consequent weight loss, insomnia, anhedonia, social withdrawal), with evident functional and social impairment (he abandoned school and stopped playing with other children), along with indicators of severity: episodes of self-mutilation (slapping his face), shouting, and running away into the forest adjacent to the village, seemingly with psychotic symptoms (paranoid delusions) that he would be captured by forest ghosts.

The mother reports that the child had a previously normal mood, interacted well with other children and at the indigenous school. He was born at term, through a normal home birth without complications, and was breastfed until 18 months of age. He shows normal neuropsychomotor development and has received complete vaccinations. There is no history of personal trauma, head trauma, CNS infections, epileptic seizures, or any other systemic medical issues. The mother used to abuse alcohol when she was young and reports having had episodes of major depression. The father abuses alcohol and cigarettes, uses illicit substances (gasoline mixed with toothpaste), and has an unstable, irritable mood and sometimes physically assaults the mother. Several of his relatives also have issues related to alcohol and cigarettes, as well as reports of mood disorders.

The anthropologists from FUNAI responsible for the community denied medical treatment for weeks, justifying that it was a "cultural problem" and, as such, should be resolved within the community itself. In Western terms, we could translate this as: "left to fend for himself." However, the psychiatric condition worsened even further, and the child attempted to drown himself in the river, but fortunately, he was stopped by another boy who witnessed the scene. The mother, going against FUNAI's decision, asked for help from a niece who knew us previously and brought the child for treatment. We received the family and, based on the transcultural phenomenological psychopathological examination, diagnosed psychotic depression. Given the family history suggestive of bipolarity, we started atypical antipsychotic medication (quetiapine 25 mg/day, titrated to 50 mg/day after 14 days) and provided psychotherapeutic support to both the child and the mother. After six days of treatment and follow-up, the child was no longer suicidal, and after three weeks, he was in a euthymic state, with no residual symptoms of psychotic depression and without any undesirable side effects. The family was instructed on the importance of continuing the treatment, including forming a therapeutic alliance with the tribal shaman responsible for the tribe, with the goal of joint treatment while respecting the community's ancestral traditions. However, after three months, the treatment was interrupted due to the difficulties in transportation imposed by those in charge of the community's health services, and we lost contact with the family, despite persistent requests made to local authorities to prevent the treatment from being discontinued.

DISCUSSION

Combining the data from the anamnesis with the psychopathological examination and considering the psychiatric history of both parents of the indigenous child reported here, the most likely diagnosis is a severe depressive episode with psychotic symptoms in the context of bipolar disorder type.[1] This illness is recognized as a major imitator, capable of mimicking several diagnoses in Child Psychiatry,

which makes its diagnosis complex and difficult, posing a challenge for non-specialists. It is one of the diseases associated with high suicide rates, requiring rapid diagnosis and intervention. The family history of mood disorders is rich, as it is a disease with a strong genetic basis and linked to a very high heritability pattern.[7]

Sociogenic theories attempting to explain the etiology of mental disorders were prevalent in the 19th century8 and, unfortunately, are still used today in a pseudoscientific manner to justify psychiatric illnesses in various settings, particularly in the context of ancestral communities exposed to Western culture9. In this regard, some anthropologists – like those mentioned in our case report – often interpret mental illness among indigenous people as a process associated with the harms brought about by contact with non-indigenous people and the increasing process of acculturation9. Our group has been debunking these false interpretations with empirical data from studies on indigenous children and adolescents, demonstrating that psychiatric illnesses, which are brain diseases, affect these ancestral communities as they do any other human group, regardless of their level of isolation.[10,11,12]

Suicide rates among Brazilian indigenous people are higher in areas where communities are more isolated, namely in the Central-West (35.6/100,000 inhabitants) and North (24.1/100,000 inhabitants) regions, with lower rates in communities located in regions with higher levels of acculturation, such as the Northeast, Southeast, and South (3.8, 4.1, and 9.7/100,000 inhabitants, respectively).[13] On the other hand, suicides predominantly occur in the gender most exposed to the acculturation process, among men. Other demographic characteristics of indigenous suicides include: they mostly occur in the 15-29 age group, among singles, with low educational levels, and predominantly by hanging.[13] It is striking that among indigenous children, the suicide rate observed is 11/100,000 inhabitants, meaning it is 18.5 times higher than that observed among non-indigenous children (0.6/100,000 inhabitants)[14,4], an alarming statistic that highlights the lack of official government intervention on a Brazilian indigenous public health issue that jeopardizes this ethnic group and its ancestral communities.

Prejudice against the diagnosis of depression, even in cultures very different from our own, and the lack of preparation to deal with these transcultural occurrences, can lead to terrible outcomes. Fortunately, a healthy encounter between asymmetric cultures, when guided by respect for their origins and ancestral values, can translate into benefits for the community, by providing access to advancements in medicine without it representing the subjugation or kidnapping of that people's cosmological essence.[15]

CONCLUSION

Indigenous children seem especially vulnerable to psychiatric disorders and suicide, even though they are more culturally isolated than adults and have less exposure to non-Indigenous culture. This serious situation and public health problem among Indigenous people are still interpreted in a romanticized, inadequate way, with a strong sociological bias, to the detriment of modern approaches to mental health based on Neurosciences.

Denying children access to treatment, regardless of or because of their ethnicity, especially when there is a threat to life, could be considered a crime under the regulations that govern the humanitarian treatment our civilization has achieved.

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SCIENTIFIC ARTICLE - SYSTEMATIC REVIEW

TREATMENT OF MYASTHENIA GRAVIS WITH RITUXIMAB: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objectives: Myasthenia Gravis (MG) is an autoimmune neuromuscular disease that is cha-racterized by muscle weakness and fatigue. Despite the availability of several therapeutic op-tions, some patients show inadequate response or intolerance to conventional treatments. In this context, rituximab emerges as a promising alternative. This study aims to analyse the effi-cacy and role of rituximab in the treatment of myasthenia gravis.

Methodology: A systematic review and meta-analysis were conducted, involving searches in the databases PubMed, EMBASE, LILACS, Cochrane Library, and Web of Science until January 2024. Studies evaluating rituximab in any dosage and infusion regimen in patients with a clinical diagnosis of myasthenia gravis were included.

Results: Of the 3188 articles initially identified, 34 studies met the inclusion criteria, totaling 725 participants. The results demonstrated that 65.7% of the patients achieved a status of mi-nimal manifestation or better on the Myasthenia Gravis Foundation of America Post-intervention Status (MGFA-PIS) scale. Additionally, the analysis revealed a significant re-duction in the dose of corticosteroids and improvements in the scores of the Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Activities of Daily Living (MG-ADL), and Myasthenia Gravis Quality of Life (MG-QoL15) scales, indicating improvement in symp-toms and quality of life.

Conclusion: Rituximab proved to be an effective alternative for controlling Myasthenia Gra-vis, significantly improving symptoms and reducing the need for corticosteroids. However, further randomized and controlled studies are needed to definitively establish its safety and efficacy in the long term.

Keywords: Meta-analysis, Myasthenia gravis, Neuromuscular junction diseases, Rituximab, Systematic review.

INTRODUCTION

The Myasthenia Gravis (MG) is an autoimmune neuromuscular disease characterized by muscle weakness and fatigability[1], resulting from antibodies against the acetylcholine receptor (anti-AChR), antibodies against muscle-specific kinase (anti-MuSK), or antibodies against low-density lipoprotein receptor-related protein 4 (anti-LRP4).[2]

Although several treatment options are available to manage this chronic condition—such as

acetylcholinesterase inhibitors, corticosteroids, and other immunosuppressive therapies[2]—some patients may show an inadequate response or intolerance to conventional treatments.

In this context, rituximab has emerged as a therapeutic option for patients with myasthenia gravis.[3]. Rituximab is a monoclonal antibody directed against CD20, a transmembrane protein found on the surface of B lymphocytes.[4]

Clinical studies and case reports have shown promising results with the use of rituximab in the treatment of myasthenia gravis.[4] B-cell depletion by rituximab[4] can reduce the production of pathogenic antibodies and modulate the immune response, leading to symptom improvement and a reduced need for corticosteroids.

However, despite these encouraging results, the use of rituximab in myasthenia gravis is still considered off-label, and further studies are needed to assess its efficacy, safety, and the best administration protocol, including dosage, frequency, and duration of treatment.

Therefore, the objective of this systematic review and meta-analysis is to review and analyze the available evidence on the use of rituximab in the treatment of myasthenia gravis, with the aim of providing a comprehensive overview of the efficacy and safety of this medication in the management of myasthenia gravis.

METHODS

This single-arm systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1 Search Strategy

Two researchers independently conducted a systematic search in the PubMed, EMBASE, LILACS, Cochrane Library, and Web of Science databases. The search was performed without date restriction, in January 2024, and included only studies in English. The search strategy was adapted for each database.

2.2 Eligibility Criteria

2.2.1 Study Type

We restricted our analysis to studies that met the following inclusion criteria: (1) published randomized and non-randomized studies; (2) studies evaluating the treatment of Myasthenia Gravis with rituximab, at any dose and infusion regimen; and (3) studies reporting outcomes of interest. Small case series with fewer than five participants and studies not published in English were excluded.

2.2.2 Participants

This study included participants who met the following eligibility criteria: clinical diagnosis of myasthenia gravis, supported by positive serology and/or electrophysiological findings; any severity grade, according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification; and all disease subtypes, based on serological classification, thymic status, and clinical phenotype. Participants under the age of 18 were excluded.

2.2.3 Outcomes of Interest

The primary outcomes evaluated were: (1) the proportion of patients who achieved minimal

manifestation (MM) status or better, according to the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) scale; and (2) the corticosteroid-sparing effect. Secondary outcomes included: (1) change in the Myasthenia Gravis Quantitative Score (QMG); (2) change in the Myasthenia Gravis Activities of Daily Living (MG-ADL) score; (3) change in the Myasthenia Gravis Quality of Life 15-Item (MG-QoL15) score; and (4) the incidence of adverse events.

2.3 Study Selection and Data Extraction

Study selection and data extraction were performed independently by two authors, following predefined search criteria and quality assessment methods. Disagreements were resolved by consensus between the two authors.

2.4 Statistical Analysis

The results for binary variables were obtained through the proportion of events, and for continuous variables, the mean difference was calculated. The analysis results were presented with a 95% confidence interval. We used the I^2 statistical test to assess heterogeneity. For outcomes with high heterogeneity ($I^2 \geq 25\%$), pooled estimates were calculated using the DerSimonian–Laird random-effects model. P-values < 0.05 were considered statistically significant. Statistical analyses were performed using the OpenMeta-analyst software.

RESULT

3.1 Study and Population Characteristics

A total of 3,188 publications were identified through the database search strategy. After removing duplicates and excluding studies based on title/abstract screening, 76 publications remained and were reviewed according to the inclusion and exclusion criteria. Thirty-four studies[5–38] were included (FIGURE 1), of which two were randomized controlled trials.[6,32]

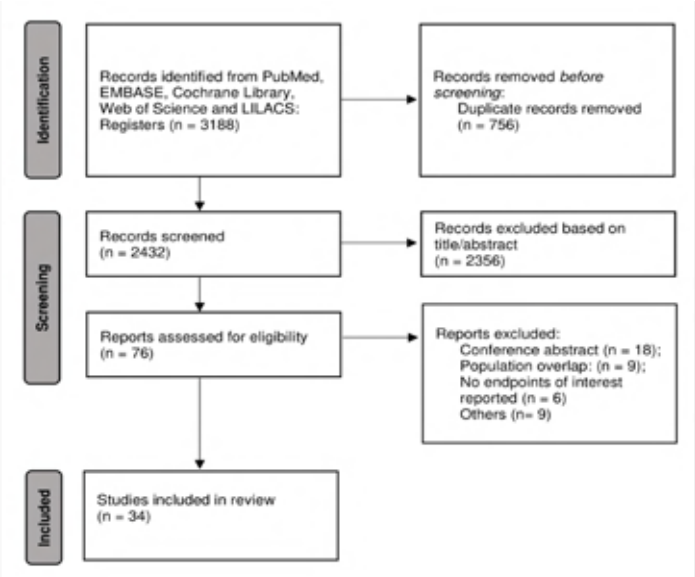

Figure 1 – PRIMSA flowchart detailing the study screening and selection process.

In total, 725 participants were included: 287 (40%) male and 438 (60%) female. Of these, 458 (63%) were anti-AChR positive, 201 (28%) anti-MuSK positive, 60 (8%) were double seronegative for anti-AChR and anti-MuSK, and 4 patients were double seropositive for anti-AChR and anti-MuSK. Thymoma was detected in 97 participants (13%) (not reported in 11 studies) (TABLE 1). The mean age at diagnosis of myasthenia gravis was 32.57 years (not reported in 11 studies), and the mean age at initiation of rituximab therapy was 38.21 years (also not reported in 11 studies). Table 2 summarizes the basic characteristics of the studies included in the systematic review.

The dose and rituximab administration regimen varied considerably among studies. The most commonly used induction protocols were: (1) 375 mg/m² weekly for 4 weeks and (2) two doses of 1000 mg administered 15 days apart.

Table 1 – General characteristics of the population

Characteristic	Total (%)
Sex	
Female	438 (60%)
Male	287 (40%)
Serology	
Anti-AChR	458 (63%)
Anti-MuSK	201 (28%)
Double seronegative	60 (8%)
Double soropositive	4 (1%)
Thymic Abnormalities	
Thymoma	97 (13%)
Total population	**725**

3.2 Efficacy Assessment

3.2.1 Proportion of Patients Who Achieved Minimal Manifestation Status or Better

Post-intervention status assessed using the MGFA-PIS scale was reported in 24 studies. We observed that 65.7% (95% CI: 0.553 – 0.761) of participants achieved minimal manifestation status or better. Heterogeneity was high (I^2 = 91.09%) (FIGURE 2).

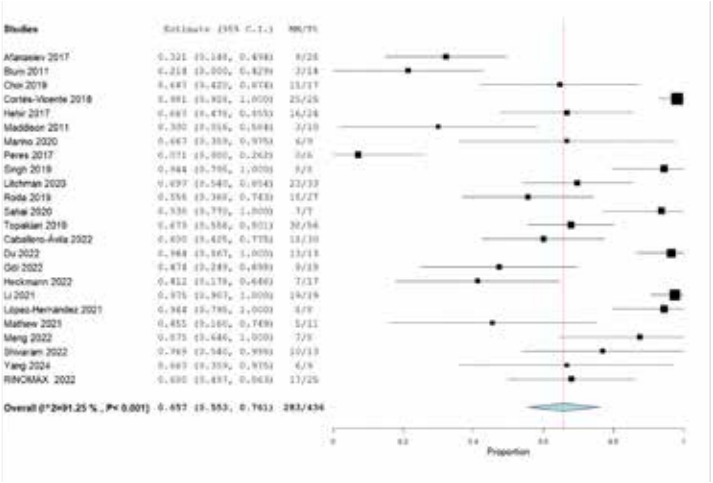

Figura 2 – Forest plot da proporção de pacientes que alcançaram um MGFA-PIS de MM ou melhor. Abreviações: CI: intervalo de confiança; MM: número de participantes que alcançaram o status de Manifestações Mínimas ou melhor; Tt: número total de participantes.

3.2.2 Corticosteroid-Sparing Effect

Corticosteroid doses were reported in thirteen studies. The average reduction in corticosteroid dose following rituximab treatment was 21.6 mg of prednisone (95% CI: 26.610 – 16.591). However, heterogeneity was high (I^2 = 80.13%) (FIGURE 3).

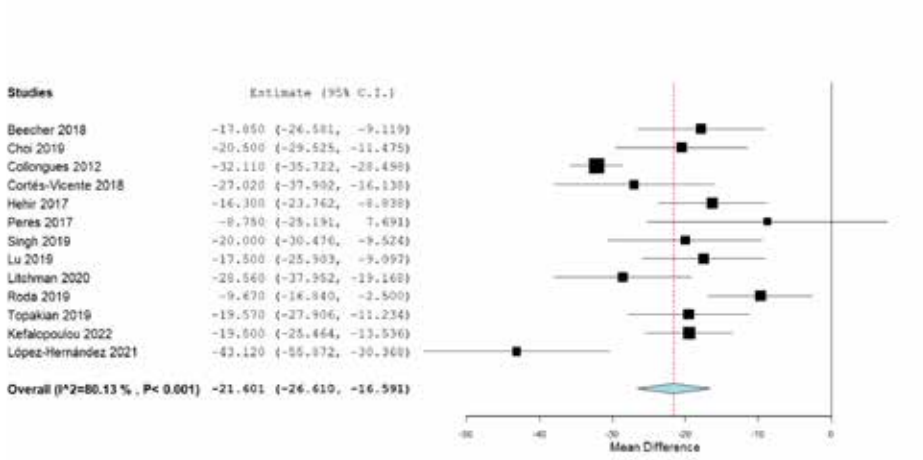

Figure 3 – Forest plot of the mean effect of rituximab therapy on corticosteroid dose reduction. Abbreviations: CI: confidence interval.

3.2.3 QMG

Six studies reported the QMG (Quantitative Myasthenia Gravis) scale. The analysis revealed a mean reduction of 8.31 points (95% CI: 10.772 – 5.863). However, heterogeneity was high (I^2 = 72.18%) (FIGURE 4).

3.2.4 MG-ADL

The MG-ADL (Myasthenia Gravis – Activities of Daily Living) scale was evaluated in four studies, which reported a reduction of 5.08 points (95% CI: 8.412 – 1.756). However, heterogeneity was high (I^2 = 91.73%) (FIGURE 4).

3.2.5 MG-QoL15

Four studies reported the MG-QoL15 (Myasthenia Gravis – Quality of Life 15-item) scale. Our analysis showed a reduction of 16.245 points (95% CI: 26.101 – 6.930). However, heterogeneity was high (I^2 = 87.04%) (FIGURE 4).

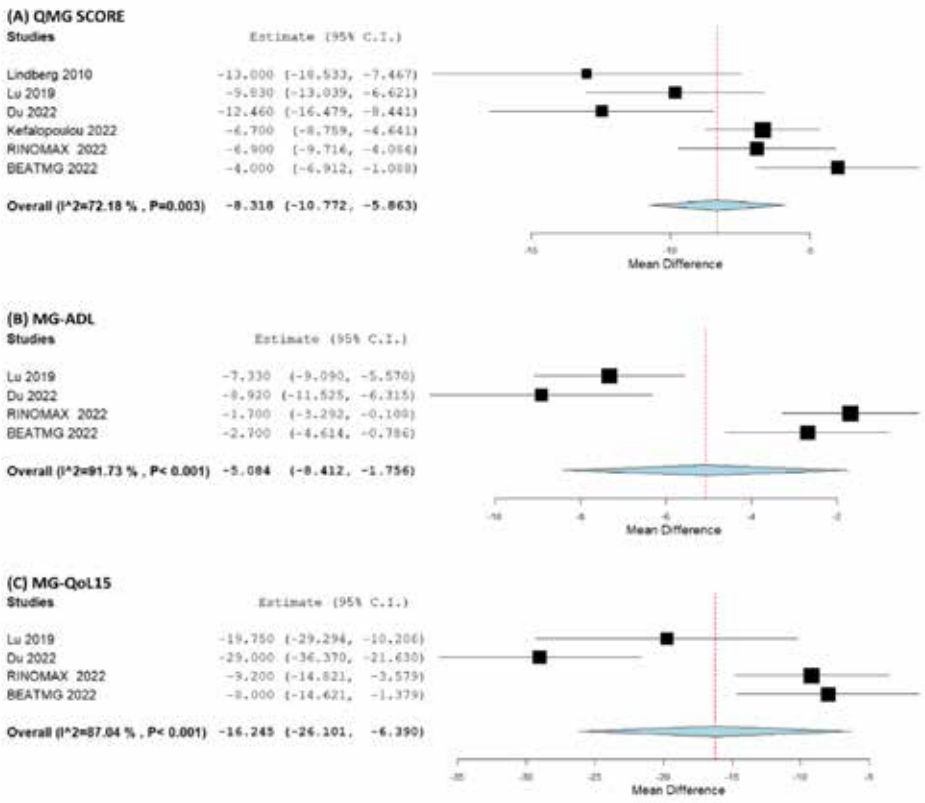

Figure 4 – (A) Forest plot of the mean difference on the Quantitative Myasthenia Gravis (QMG) scale; (B) Forest plot of the mean difference on the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale; (C) Forest plot of the mean difference on the Myasthenia Gravis-Quality of Life 15 (MG-QoL15) scale. Abbreviations: CI: confidence interval.

3.3 Safety

A total of 257 adverse events were reported, 57 of which were classified as serious adverse events. Among the serious adverse events, one case of progressive multifocal leukoencephalopathy (PML) was documented.

DISCUSSION

Several studies have already reported the use of rituximab in the treatment of Myasthenia Gravis; however, most of these are observational. Two randomized studies—RINOMAX[32] and BEAT-MG Phase II[6]—were published in 2022 and provided more robust data regarding the use of rituximab in MG treatment. Current guidelines support rituximab as a therapeutic option for refractory MG.[3] Moreover, recent evidence suggests the possibility of its use as a first-line therapy in anti-MuSK-positive patients.[3]

In this systematic review, 34 studies[5–38] were included, of which two were randomized[6,32] and 94.12% were non-randomized[5,7–31,33–38]. These studies included participants with refractory MG, non-refractory MG, and individuals considered naïve to corticosteroid-sparing immunotherapy. Additionally,

participants with different MG subtypes were included, based on serological profile, age of disease onset, and thymic status.

In our meta-analysis, we found that 65.7% of patients achieved minimal manifestation (MM) status or better on the MGFA-PIS scale. A previous meta-analysis reported similar data, with 64%[39] of patients reaching minimal manifestation status or better.

The efficacy of rituximab therapy in MG patients was also evaluated using the QMG and MG-ADL scales, showing a mean reduction of 8.31 and 5.08 points, respectively, after the intervention—demonstrating improvement in both symptoms and disease severity. A previous meta-analysis also reported a reduction in QMG score post-intervention, with a standardized mean difference of -1.55[39].

The impact of rituximab treatment on the quality of life of individuals with myasthenia gravis was assessed using the MG-QoL15 scale, with a mean reduction of 16.245 points, indicating an improvement in quality of life.

Another very important goal in treating patients with myasthenia gravis is reducing the need for corticosteroids. The results of this meta-analysis showed a mean reduction of 21.6 mg of prednisone with rituximab treatment. A previous meta-analysis also showed a reduction in corticosteroid doses, with a standardized mean difference of -1.46.[39]

However, in contrast to the results of this meta-analysis, the randomized, double-blind, placebo-controlled study BEAT-MG[6], conducted in anti-AChR-positive MG patients, did not demonstrate a statistically significant corticosteroid-sparing effect of rituximab compared to placebo. Moreover, the study did not show a statistically significant clinical improvement.

RINOMAX[32] is another randomized, double-blind, placebo-controlled study—composed predominantly of anti-AChR-positive patients (92%)—and was published in 2022. In this study, the group treated with rituximab showed a higher percentage of patients achieving minimal manifestation status (71%) compared to the placebo group (29%), thus meeting the primary endpoint. Additionally, the rituximab group required fewer hospitalizations and rescue therapies, as well as lower corticosteroid doses. Despite these benefits, the study did not demonstrate a significant reduction in QMG and MG-ADL scores.

This discrepancy between results may be attributed to the significant heterogeneity in study populations and methodologies, further reinforcing the need for new randomized clinical trials.

The studies included in this systematic review and meta-analysis employed a variety of therapeutic protocols, as there is no established protocol for the use of rituximab in MG. Among the induction regimens, the most frequently used were 375 mg/m² weekly for 4 weeks and two doses of 1000 mg administered 15 days apart, which are regimens already used in other conditions.[40,41] The frequency and criteria used to indicate maintenance/reinfusion doses also varied, with doses given at fixed intervals or based on clinical and/or laboratory criteria. The lack of an optimized protocol for MG may affect the outcomes of this therapy; therefore, new evidence is needed to determine the most effective dosing regimen.

Overall, rituximab was well tolerated by participants. However, there was one case of PML (progressive multifocal leukoencephalopathy), a severe condition caused by reactivation of the JC virus, which has a high mortality rate. The patient diagnosed with PML died. There is substantial evidence supporting the safety of rituximab in immune-mediated and hematologic diseases.[40,41,42] This medication is considered safe, with only a small percentage of patients experiencing serious adverse effects[9,40,42]. The results from the BEAT-MG study further support the safety of rituximab in MG.[6]

Despite the observed impact on standardized scales—MGFA-PIS, QMG, MG-ADL, MG-QoL15—and the corticosteroid-sparing effect, the results of this study presented considerable heterogeneity. This heterogeneity may be associated with the wide diversity of the study population, which included patients with

varying serological profiles, age of disease onset, thymic alteration status, and refractoriness to conventional immunotherapy, as well as different pre-intervention clinical statuses, various infusion protocols, and different follow-up durations.

Another limitation of this study is the inability to clearly identify which subgroups respond best to rituximab, although current data already suggest greater benefit in anti-MuSK-positive patients[3]. The single-arm nature of this meta-analysis is also a limitation, but this characteristic reflects the design of most of the included studies.

Therefore, it is essential to conduct large randomized clinical trials to evaluate the efficacy and safety of rituximab in the context of myasthenia gravis.

In conclusion, there is a growing body of literature indicating the benefit of rituximab therapy in MG, which, in this meta-analysis, is evidenced by improvements in standardized scales—MGFA-PIS, QMG, MG-ADL, MG-QoL15—as well as by its corticosteroid-sparing effect.

Table 2 – Characteristics of included studies. Abbreviations: H: male; F: female; DSN: double seronegative; SD: standard deviation; MGFA-PIS: Myasthenia Gravis Foundation of America Post-intervention Status; MM: minimal manifestation status; NR: not randomized; R: randomized; ND: not available; DSP: double seropositive.

STUDY	TYPE OF STUDY	SAMPLE SIZE	SEX M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	ANTIBODIES AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; ≥ MM
AFANASIEV, 2017[25]	NR	28	13 (46%) / 15 (54%)	50.6 (12.0)	21 / 3 / 4	**Induction:** 1000 mg on Day 1 and Day 15 or 375 mg/m² weekly for 4 weeks. **Maintenance:** 1000 mg or 375 mg/m² every 6 months..	9
BEATMG (2022)[9]	R	25	14 (56%) / 11 (44%)	53.2 (17.5)	25 / 0 / 0	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** 375 mg/m² weekly for 4 weeks in the sixth month.	ND
BEECHER, 2018[7]	NR	22	12 (55%) / 10 (45%)	49.4 (13.4)	10 / 9 / 3	**Induction:** 375 mg/m² weekly for 4 weeks, followed by 2 infusions every 4 weeks, or 750 mg on Day 1 and Day 15. **Maintenance:** 2 doses of 750 mg/m² (up to a maximum of 1 g per dose) with a 2-week interval, depending on clinical status.	ND
BLUM, 2011[8]	NR	14	5 (36%) / 9 (64%)	51.14 (18.42)	11 / 3 / 0	**Induction:** 500 mg on Day 1 and Day 15. **Maintenance:** if B-cell count exceeds 1% in two measurements associated with clinical signs of worsening.	3
BRAUNER, 2020[9]	NR	72	41 (57%) / 31 (43%)	60 (18)	60 / 0 / 12	**Induction:** single infusion of 500 mg (n = 57), 100 mg (n = 12), or 1000 mg (n = 3). **Maintenance:** 500 mg every 6 months or 100 mg (n = 3).	ND
CABALLERO-ÁVILA, 2022[10]	NR	30	3 (10%) / 27 (90%)	40.9 (19.3)	18 / 12 / 0	**Induction:** 375 mg/m² weekly for 4 weeks, followed by 1 monthly dose for 2 months. **Maintenance:** according to clinical status.	18
CHOI, 2019[11]	NR	17	11 (65%) / 6 (35%)	50.52 (15.55)	9 / 6 / 2	**Induction:** 375 mg/m² on Day 1 and Day 15. **Maintenance:** single infusion of 375 mg/m², based on B-cell frequency and clinical status.	11
COLLONGUES, 2012[12]	NR	20	9 (45%) / 11 (55%)	ND	12 / 4 / 3 *(1 DSP)	**Induction:** 375 mg/m² weekly for 4 weeks or 1000 mg on Day 1 and Day 15. **Maintenance:** 375 mg/m² every 3 months or 1000 mg depending on clinical status.	ND
CORTÉS-VICENTE, 2018[13]	NR	25	1 (4%) / 24 (96%)	51.34 (15.82)	0 / 25 / 0	**Induction:** 375 mg/m² weekly for 4 weeks, followed by 375 mg/m² monthly for 2 months, or 1000 mg on Day 1 and Day 15, or 375 mg/m² weekly for 4 weeks. **Maintenance:** according to clinical status.	25

STUDY	TYPE OF STUDY	SAMPLE SIZE	SEX M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	ANTIBODIES AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; ≥MM
DOS SANTOS, 2020[14]	NR	29	12 (41%) / 17 (59%)	49.6 (16.3)	20 / 5 / 4	**Protocol A:** two infusions of 1 g spaced 2 weeks apart, followed by 1 g every 6 months (N = 22). **Protocol B:** two infusions of 1 g spaced 2 weeks apart and one infusion at 6 months. Reinfusions according to clinical status (N = 3). **Protocol C:** 375 mg/m² weekly for 4 weeks. Reinfusions according to clinical status (N = 1). **Protocol D:** 1 g infusion every 2 months for 1 year, then 1 g every 6 months (N = 3).	ND
DOUGHTY, 2021[15]	NR	40	22 (55%) / 18 (45%)	55.5 (18.1)	28 / 9 / 3	**Induction:** 1000 mg × 2 or 375 mg/m² × 4. **Maintenance:** reinfusion in 31 patients.	ND
DU, 2022[16]	NR	13	6 (46%) / 7 (54%)	ND	13 / 0 / 0	**Induction:** 100 mg weekly for a maximum of 3 weeks. **Maintenance:** 100 mg according to clinical status and CD19+ lymphocyte population.	13
FATEHI, 2021[17]	NR	34	12 (35%) / 22 (65%)	47.9 (15.2)	17 / 9 / 8	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** 1000 mg every 6 months.	ND
GÖL, 2022[18]	NR	19	10 (53%) / 9 (47%)	48.6 (12.3)	10 / 6 / 1 (*2 DSP)	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** 1000 mg every 6 months, depending on clinical status.	9
HECKMANN, 2022[19]	NR	17	1 (6%) / 16 (94%)	36.38 (15.17)	10 / 5 / 2	**Induction:** Single infusion of 375 mg/m².	7
HEHIR, 2017[20]	NR	24	3 (13%) / 21 (88%)	ND	0 / 24 / 0	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** 375 mg/m² weekly for 4 weeks or 2 doses of 1000 mg with a two-week interval.	16
KEFALOPOULOU,2022[21]	NR	30	10 (33%) / 20 (67%)	ND	16 / 6 / 8	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** 375 mg/m² weekly for 2 weeks every 6–8 months (AChR+) or 375 mg/m² weekly for 2 weeks based on clinical status (MuSK+).	ND
LI, 2021[22]	NR	19	7 (37%) / 12 (63%)	ND	19 / 0 / 0	The mean dose per Rituximab cycle was 183 mg (range: 100–400 mg). Reinfusion depends on the CD19+ lymphocyte population, with a mean interval of 6.9 months.	19
LINDBERG, 2010[23]	NR	5	2 (40%) / 3 (60%)	ND	5 / 0 / 0	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** 2 doses of 1000 mg with a two-week interval (in some patients).	ND

STUDY	TYPE OF STUDY	SAMPLE SIZE	SEX M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	ANTIBODIES AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; ≥ MM
LITCHMAN, 2020[24]	NR	33	9 (27%) / 24 (73%)	ND	17 / 16 / 0	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** 375 mg/m² weekly for 4 weeks every 6 months.	23
LÓPEZ-HERNÁNDEZ, 2021[25]	NR	8	2 (25%) / 6 (75%)	ND	8 / 0 / 0	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** 1000 mg every 6 months, depending on clinical response.	8
LU, 2019[26]	NR	12	2 (17%) / 10 (83%)	30.6 (29.6)	12 / 0 / 0	**Induction:** 600 mg as a single infusion. **Maintenance:** 600 mg every 6 months (at 6 and 12 months).	ND
MADDISON, 2011[27]	NR	10	0 (0%) / 10 (100%)	32.7 (12.21)	7 / 3 / 0	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** monthly infusion in three patients.	3
MARINO, 2020[28]	NR	9	1 (11%) / 8 (89%)	50.4 (12.8)	0 / 9 / 0	**Induction:** 375 mg/m² weekly for 4 weeks, followed by one dose of 375 mg/m² after 3 months.	6
MATHEW, 2021[29]	NR	11	9 (82%) / 2 (18%)	50.54 (18.71)	11 / 0 / 0	**Induction:** 500 mg on Day 1 and Day 15; three patients received an additional 500 mg dose two weeks later due to clinical worsening. **Maintenance:** 500 mg every 6–12 months, depending on clinical status.	5
MENG, 2022[30]	NR	8	8 (100%) / 0 (0%)	ND	0 / 8 / 0	**Induction:** 375 mg/m² on Day 1 and Day 15 or a single infusion of 375 mg/m². **Maintenance:** according to clinical status.	7
PERES, 2017[31]	NR	6	1 (17%) / 5 (83%)	62.0 (16)	4 / 0 / 2	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** according to clinical status, CD19+ lymphocyte population, and immunoglobulin levels, with a minimum interval of 4 months.	0
RINOMAX, 2022[32]	R	25	18 (72%) / 7 (28%)	67.4 (13.4)	23 / 0 / 0	**Induction:** single infusion of 500 mg.	17
RODA, 2019[33]	NR	27	5 (19%) / 22 (81%)	41.85	10 / 13 / 4	**Induction:** 375 mg/m² weekly for 4 weeks or 1000 mg in weeks 1 and 3. **Maintenance:** according to clinical status.	15
SAHAI, 2020[34]	NR	7	2 (29%) / 5 (71%)	ND	7 / 0 / 0	**Induction:** 375 mg/m² weekly for 4 weeks, or 1000 mg on Day 1 and Day 15, or a single infusion of 1000 mg. **Maintenance:** every 6–12 months in three patients.	7
SHIVARAM, 2022[35]	NR	13	6 (46%) / 7 (54%)	44.84 (15.73)	10 / 1 / 1 (*1 DSP)	**Induction:** 375 mg weekly for 1–4 weeks or 1000 mg on Day 1 and Day 15. **Maintenance:** 500–600 mg depending on the	10

STUDY	TYPE OF STUDY	SAMPLE SIZE	SEX M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	ANTIBODIES AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; ≥ MM
						CD19+/CD20+ lymphocyte population, with a minimum interval of 3 months.	
SINGH, 2019[36]	NR	8	7 (88%) / 1 (13%)	38.12 (11.94)	6 / 2 / 0	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** 375 mg/m² weekly for 4 weeks every 6 months.	8
TOPAKIAN, 2019[37]	NR	56	22 (39%) / 34 (61%)	51.01 (20.13)	39 / 14 / 3	**Induction:** 375 mg/m² on Day 1 and Day 15, or 500 mg on Day 1 and Day 15, or 1000 mg on Day 1 and Day 15; other protocols used in 9 patients. **Maintenance:** based on B-cell population or clinical status.	38
YANG, 2024[38]	NR	9	1 (11%) / 8 (89%)	ND	0 / 9 / 0	**Induction:** 500 mg divided over three consecutive days (100 mg on Day 1, 200 mg on Days 2 and 3). **Maintenance:** 500 mg every 6–12 months.	6

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EDITORIAL AND REVIEW

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SCIENTIFIC ARTICLE - NARRATIVE REVIEW

ULTRASOUND IN THE DIAGNOSIS OF ENDOMETRIOSIS: AN INTEGRATIVE REVIEW

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ABSTRACT

Transvaginal ultrasonography (TVUS) has established itself as an essential tool in the diagnosis of endometriosis, standing out for its high sensitivity and specificity, especially in the identification of endometriomas. Its low cost and wide availability make it the first-choice exam for the initial detection of the disease, being able to map ovarian, pelvic and deep lesions. However, it has limitations in the identification of small lesions or in areas of difficult access, in addition to depending on the experience of the operator. Given these limitations, magnetic resonance imaging emerges as a complementary exam, providing a more detailed evaluation in complex cases and in preoperative planning. TVUS, however, has advantages over MRI in the detection of small peritoneal and intestinal lesions and in the assessment of pelvic mobility. Ultrasonography allows a detailed analysis of the distribution of lesions, aiding in surgical planning and in the formation of multidisciplinary teams for more serious cases. In addition, it plays a fundamental role in the surveillance of pregnant patients, helping to differentiate decidualized endometriomas from ovarian tumors. Finally, TVUS plays an essential role in personalizing treatment and monitoring endometriosis, contributing to early diagnosis and improving patients' quality of life.

Keywords: Imaging Diagnosis, Endometriosis, Endometrioma, Review, Ultrasonography.

INTRODUCTION

Transvaginal ultrasonography (TVUS) has become established as one of the main diagnostic tools for endometriosis, particularly due to its high sensitivity and specificity in identifying endometriomas. With its affordable cost and wide availability, TVUS has been the first-line choice in various clinical protocols, being capable of mapping ovarian lesions, pelvic anatomical features, and even deeper lesions, such as those involving the uterosacral ligaments and the rectovaginal septum. However, despite its effectiveness and popularity, the use of TVUS in endometriosis is not without limitations, especially when it comes to small lesions or those located in hard-to-reach areas, such as the intestines or extraperitoneal sites.

Moreover, the interpretation of the results depends heavily on the operator's experience, which may affect the accuracy of the examination in less specialized centers.[1,2]

Although TVUS is capable of providing crucial information for the initial detection of the disease, its ability to fully characterize the extent of endometriosis—particularly in cases of deep endometriosis or when multiple anatomical compartments are involved—may be limited. In this context, the combination of ultrasonography with other imaging modalities, such as Magnetic Resonance Imaging (MRI), has been advocated, as it offers a more comprehensive and accurate view of the disease. This narrative review aims to explore the available evidence regarding the role of TVUS in the diagnosis and clinical management of endometriosis, addressing its benefits and limitations, and discussing its integration with other diagnostic tools.[2]

METHODS

This narrative review aims to evaluate the role of transvaginal ultrasonography (TVUS) in the diagnosis and clinical management of endometriosis. For the selection of studies, articles published between 2005 and 2025 in English, Portuguese, and Spanish were included, provided they discussed the application of ultrasonography in the assessment of endometriosis. The literature search was conducted in the PubMed, Scopus, Google Scholar, and LILACS databases, using keywords such as "endometriosis," "transvaginal ultrasonography," "diagnostic imaging," among other related terms. Only studies that directly addressed the use of transvaginal ultrasonography in the identification of endometriosis were considered for this review, including clinical trials, systematic reviews, and guidelines. Articles addressing alternative diagnostic methods, other gynecological conditions, or studies conducted in non-human populations were excluded.

DISCUSSION

The clinical suspicion associated with the physical examination raises the hypothesis of endometriosis, but the use of additional diagnostic tools is necessary. Pelvic and transvaginal ultrasound with bowel preparation and magnetic resonance imaging with specialized protocols are the main imaging methods for the detection and staging of endometriosis and should be performed by professionals experienced in this diagnosis.[1]

The first imaging exam to be requested based on a suggestive physical examination is the transvaginal pelvic ultrasound. It has high sensitivity and specificity in identifying endometriomas (83% and 89%, respectively). In cases of endometriosis of the uterosacral ligaments, rectovaginal septum, and vagina, the overall sensitivity and specificity are 53% and 93%, respectively.[1] If the exam is conclusive, treatment can be indicated without the need for additional imaging tests.

Diagnostic methods used in the investigation of endometriosis have been extensively studied in recent decades, especially transvaginal ultrasound (TVUS), which, when performed at specialized centers and by experienced professionals, has shown high accuracy in diagnosing the disease.[2-4] Additionally, some centers advocate the use of techniques that enhance this diagnostic capability, such as vaginal distension with gel and bowel preparation with laxatives.[5-8]

Due to the high accuracy and greater accessibility of ultrasound compared to magnetic resonance imaging, TVUS is currently considered the first-line method for diagnosing the disease, capable of mapping and characterizing lesions with high precision, including in the extraperitoneal compartment. These characteristics support the recent shift in the role of laparoscopy, which is no longer considered

the gold standard method and is usually performed only for treatment in patients previously diagnosed by specialized imaging tests.[9,10]

The role of ultrasound (USG) goes beyond diagnosis. Detailed knowledge about the distribution and characteristics of deep endometriosis (DE) lesions in patients' organs is of utmost relevance for assessing surgical risk, preoperative counseling, and team planning. This enables, for example, the organization of a multidisciplinary team including a colorectal surgeon when there is deep intestinal involvement or a urologist when there is urinary system involvement, increasing the opportunities to provide a unified and potentially curative approach, with positive effects on the quality of life of those patients indicated for surgery.[9,11,12]

This explains why detailed imaging exams are important for guiding the procedure and can even prevent some lesions hidden from laparoscopy from being overlooked, such as those located in the extraperitoneal compartment.[13]

In 2020, important societies such as the European Society for Gynaecological Endoscopy, the European Society of Human Reproduction and Embryology, and the World Endometriosis Society published recommendations on surgical techniques and highlighted the importance of imaging methods for the proper planning of these procedures in the preoperative phase of deep endometriosis.[14]

Some authors consider ultrasound superior to MRI in detecting small peritoneal and intestinal lesions, as well as vesical nodules.[4,15]

Ultrasound offers an advantage in the evaluation of pelvic organ adhesions, as it allows for the assessment of the dynamic mobility of structures upon palpation through the probe. This method is also better at identifying small intestine lesions, particularly those located near the sigmoid and the ileocecal region, where the peristaltic movements of the intestine can hinder analysis by magnetic resonance imaging.[16] The assessment of incipient lesions in the uterosacral ligaments is more difficult with MRI, as these ligaments tend to show signals similar to endometriotic tissue. On the other hand, in ultrasound, the pathological tissue has low echogenicity, contrasting with the normal tissue, which facilitates the detection of minute lesions.[5,17,18]

In contrast, MRI is better at identifying smaller ovarian lesions compared to ultrasound and distinguishing endometriomas from other adnexal lesions, such as hemorrhagic cysts or neoplasms. Magnetic resonance imaging also has the advantage of identifying and mapping deep endometriosis lesions that affect the pelvic wall and the nerve roots from the sacral plexus.[16,19]

Researchers and guidelines suggest that transvaginal ultrasound (TVUS) should be the first-line study when there is suspicion of endometriosis, as it is not only low-cost but also easily accessible and well-tolerated by patients.[10,20] Therefore, MRI could be reserved for the evaluation of more complex specific cases and for pre-surgical staging.[10]

When comparing TVUS with transrectal ultrasound, both are equivalent in diagnosing and detailing lower intestinal lesions; however, the former is superior both in detecting extraintestinal lesions and in intestinal lesions above the rectosigmoid, factors that have led to the current disuse of the latter for this purpose.[15]

The analyses conducted by Chapron et al. (2019), when studying laparoscopic findings of the anatomical distribution of deep endometriosis lesions in the abdomen, made a significant contribution to the understanding of the disease's behavior.[9]

However, the difficulties faced by surgeons and the potential surgical risks highlighted the need for the development of non-invasive methods for this purpose, such as ultrasound. During this period, the

first studies on the subject were initiated by Bazot,[21] highlighting the high accuracy of TVUS in detecting endometriosis, particularly for the intestinal The pelvic location of the disease can be described according to three compartments: anterior, middle, and posterior.and vesical foci of the disease.[22]

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CENTRAL COMPARTMENT

The typical ultrasonographic characteristic of an endometriotic cyst located within the ovary, known as an endometrioma, is a unilocular cyst with a ground-glass appearance and no vascularization on color Doppler. It may, however, appear as unilocular solid cysts or multilocular solid cysts with papillary projections, or as a multilocular cyst.[23]

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The multilocular morphology may arise from multiple endometriomas in the same ovary. There are reports that the ultrasonographic appearance of endometriomas differed between premenopausal and postmenopausal patients.[24,25] Endometriomas in postmenopausal patients were less frequently unilocular cysts and less likely to exhibit a ground-glass echogenicity (Figure 1).[25]

Ovarian mobility can be assessed by applying pressure to the ovaries using the endocavitary probe and by simultaneously applying abdominal pressure during the bimanual examination. Immobile ovaries are considered a soft marker of pelvic endometriosis. The operator should visualize the mobility of the ovaries against the lateral pelvic wall, against the uterus medially, against the uterosacral ligaments inferiorly, and against all other pelvic organs. Bilateral ovarian fixation behind the uterus is known as "kissing ovaries."[25]

In the presence of endometriosis in the fallopian tube, a dilated tube with thick walls and incomplete septa can be observed, with dense liquid content (hematosalpingitis) in cases of endoluminal pathology or with anechoic content (hydrosalpinx) in cases of obliteration due to adhesions.[25]

ANTERIOR COMPARTMENT

The anterior compartment is composed of the urinary bladder, uterovesical septum, and ureters. On ultrasound, bladder endometriosis appears as a hypoechoic lesion with or without regular protruding contours toward the lumen, involving the serosa, muscular layer, or submucosa of the bladder. The term bladder endometriosis should be used only when there is infiltration of the bladder wall and not in cases of adhesions or superficial peritoneal implants on the bladder serosa.[25]

During the examination, using a longitudinal cut through the cervical os and moving the probe toward the lateral pelvic wall, it is possible to assess the distal part of the ureter adjacent to the vesical trigone, in order to evaluate the presence of stenosis and consequent cephalic dilation of the pelvic ureters. This finding may suggest direct invasion or compression of the ureter by endometriotic nodules, ovarian endometriomas, or adhesions.[25]

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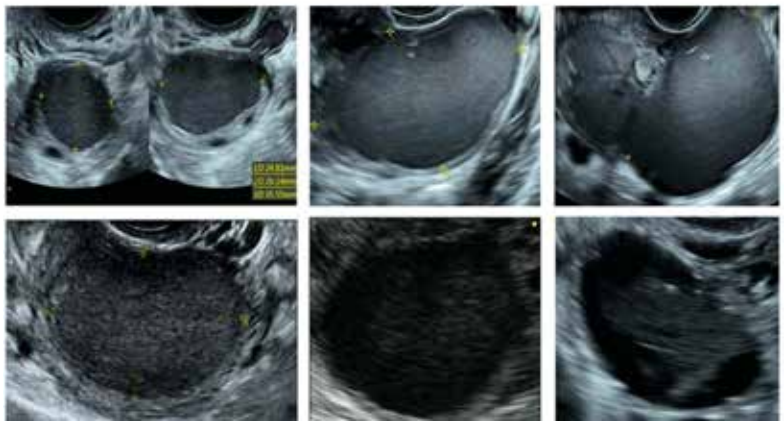

FIGURE 1. Grayscale images of typical ultrasonographic endometriomas: unilocular cysts with a ground-glass appearance inside the ovary.[25]

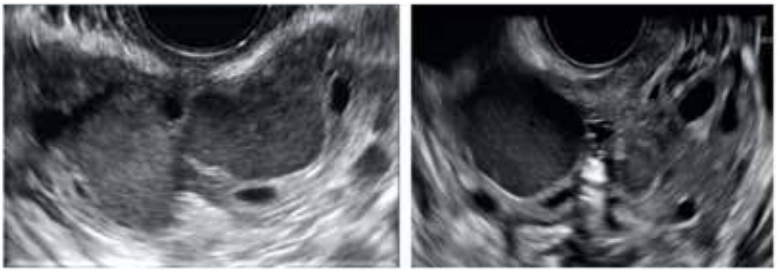

FIGURE 2. Grayscale image of kissing ovaries.[25]

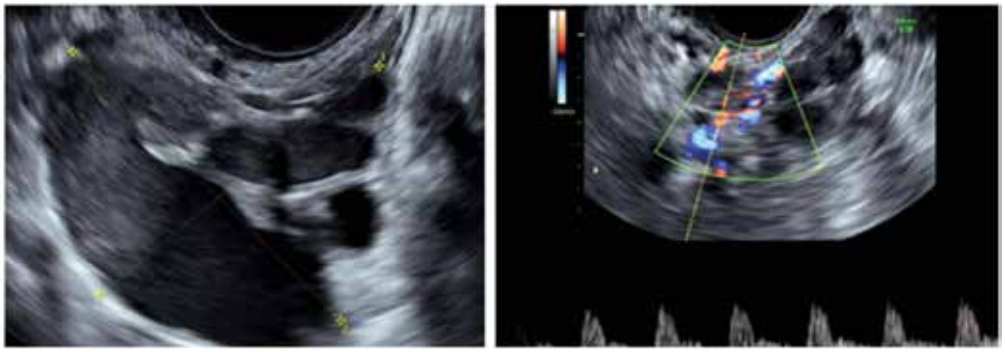

FIGURE 3. Ultrasonographic images of fallopian tube endometriosis showing a dilated tube with thick walls, incomplete septa, and dense liquid content.[25]

POSTERIOR COMPARTMENTS

The most common sites of deep infiltrative endometriosis in the posterior compartment are: posterior vaginal fornix/rectovaginal septum, uterosacral ligaments, anterior rectum/rectosigmoid junction, and sigmoid colon.[9]

The ultrasonographic characteristics of deep infiltrative endometriosis nodules were systematically defined by the International Deep Endometriosis Analysis Group. According to this classification, involvement of the rectovaginal septum should be suspected when an endometriotic nodule, appearing as a hypoechoic solid nodule with smooth or irregular contours, is seen in the rectovaginal space below the line that passes along the lower edge of the posterior cervical lip. An isolated rectovaginal septum nodule is rare and is usually an extension of the posterior vaginal wall, anterior rectal wall, or involvement of both the posterior vaginal wall and anterior rectal wall. Hourglass-shaped nodules may occur when vaginal fornix endometriosis lesions extend to the anterior rectal wall.[22,23,24]

The uterosacral ligaments affected by deep infiltrative endometriosis are characterized by the presence of hypoechoic tissue with regular/irregular margins within the peritoneal fat surrounding the uterosacral ligaments.[25]

The anterior rectum, the rectosigmoid junction, and the sigmoid colon are the areas most commonly affected in the posterior compartment. During the assessment of the posterior compartment, a negative

sliding sign (Sliding Test) between the rectosigmoid and the uterus could indicate obliteration of the Douglas pouch, while hypoechoic tissue altering the hyperechoic layer between the vagina and rectum highlights the presence of deep infiltrative endometriosis in the rectovaginal septum (Table 1).[25]

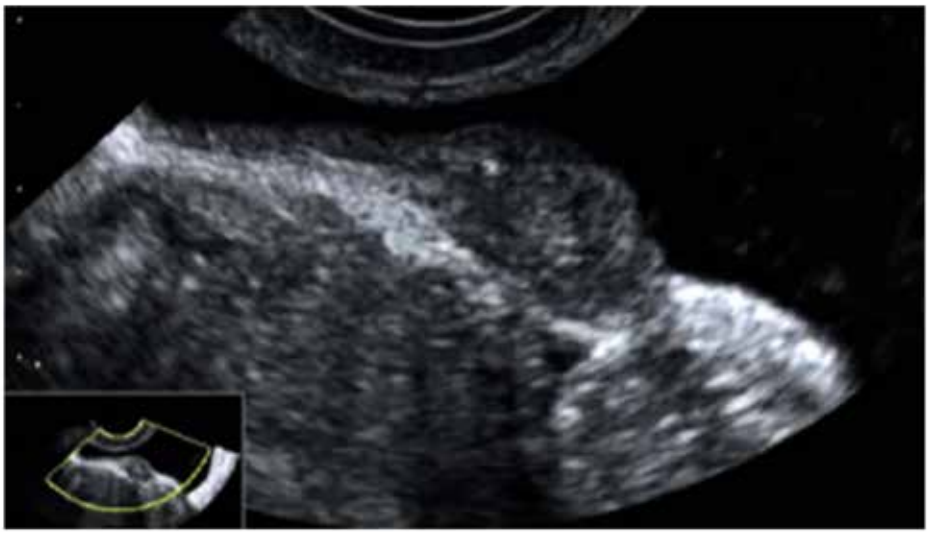

FIGURE 4. Ultrasound image showing a hypoechoic nodule on the bladder wall.[25]

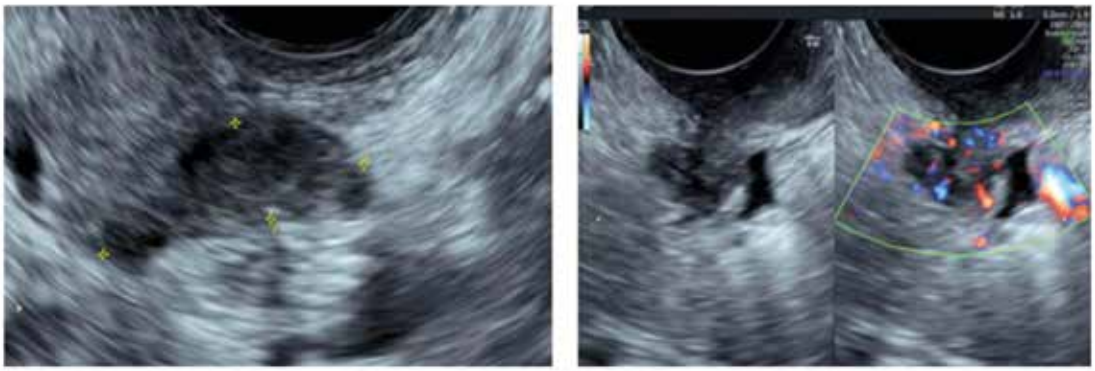

FIGURE 5. Ultrasound images of endometriotic nodules involving the uterosacral ligaments.[25]

TABLE 1. Ultrasonographic features of endometriosis.

PATHOLOGY	ULTRASONOGRAPHIC CHARACTERISTICS
Adenomyosis	• Globular shape • Enlarged dimensions of the uterus • Uterine wall asymmetry unrelate to leiomyoma • Presence of an indistinctly defined area with either descreased or increased echogenicity • Hypoechoic linear striations • Round anechoic areas of 1-7 mm diameter (myometrial cysts) • Adenomyotic lesion • Irregularities of the endometrial-myometrial junctional zone
Endometrioma	• Unilocular cyst (most commonly), multilocular, unilocular-solid, multilocular-solid (less commonly) • Ground-glass content • No vascularization on color Doppler
Deep infiltrating endometriosis	• Hypoechoic lesion with or without regular contours) • Hourglass-shaped or diabolo-like nodule appearance • Comet nodule appearance • Trickened and hyperechoic uterosacral ligaments
Decidualized endometrioma	• Unilocular-solid or multilocular-solid • Ground-glass or low-level cyst content • Rounded papillary projections with smooth surface • Well vascularized

IMPORTANCE OF ULTRASOUND IN THE TREATMENT OF ENDOMETRIOSIS

Ultrasonographic evaluation is of utmost importance in planning the timing and type of surgical procedure to be performed. Morphological representation, along with patient characteristics (age, symptoms, and desire for pregnancy), allows doctors to plan the best personalized treatment. It is known that approximately 30% to 50% of women with endometriosis become infertile. Therefore, effective evaluation of the normal residual ovarian parenchyma can allow for better preoperative counseling to avoid this outcome.[25]

In cases of deep pelvic endometriosis, the distribution of pelvic disease is becoming increasingly important. While patients with vesical endometriosis are usually symptomatic (frequency, urgency, and dysuria), women with ureteral endometriosis are often asymptomatic, leading to silent obstruction of the urinary tract and loss of renal function. In this scenario, ultrasonographic diagnosis of ureteral endometriosis with hydroureter and hydronephrosis plays a crucial role in planning the best surgical procedure.[25]

Another important issue is monitoring during pregnancy. During this period, endometriomas can undergo significant morphological changes, referred to as decidualization. This is a process in which endometrial alterations caused by high levels of progesterone increase epithelial glandular secretion, glycogen accumulation, and stromal vascularization.[25]

The most common appearance of decidualized endometriomas is a solid unilocular or multilocular ovarian mass with ground-glass content or low-level cysts, featuring rounded, well-vascularized papillary projections with a smooth surface. This appearance enables clinicians to distinguish a decidualized endometrioma from a borderline tumor, where the papillary projections typically have an irregular surface.[25]

In this context, women diagnosed with endometriomas via ultrasound before pregnancy are treated conservatively, and ultrasound monitoring is essential to understand the morphological cases. However,

the management of ovarian cysts during pregnancy remains a challenge, and ultrasound diagnosis may sometimes be inconclusive.[25]

CONCLUSION

Ultrasound plays a crucial role in the diagnosis of endometriomas, as well as in the identification and localization of pelvic endometriosis. The ability to accurately recognize and map endometriosis in the pelvis allows for personalized patient treatment. Additionally, the examination plays an essential role in the monitoring of patients with specific conditions, such as during pregnancy, leading to better management of this patient subgroup. Finally, it is of utmost importance to expand the use of imaging exams in routine consultations to increase the early diagnosis of endometriosis and, consequently, provide more appropriate treatment.

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EDITORIAL AND REVIEW

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SCIENTIFIC ARTICLE - INTEGRATIVE REVIEW

INCORPORATION OF ROBOTIC SURGERY INTO GENERAL SURGERY PRACTICE: BENEFITS, CHALLENGES, AND FUTURE PERSPECTIVES

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ABSTRACT

Robotic surgery has emerged as a revolutionary technology in contemporary surgical practice, initiating a new era for surgeons across various specialties. This article presents an integrative literature review that aims to analyze the benefits, challenges, and perspectives of robotic assistance specifically in general surgery. The objective was to gather and synthesize recent scientific evidence regarding the impact of this technique on surgical practice, highlighting both its advantages and the limitations encountered. The methodology was based on the criteria proposed by Whittemore and Knafl, with a search performed in the PubMed database using predefined inclusion and exclusion criteria. Ten articles published between 2019 and 2024 were selected. The findings indicate that robotic procedures offer numerous benefits for both patients and healthcare professionals. However, relevant limitations persist, particularly related to the high operational costs and the need for specialized technical skills to handle the equipment. Nevertheless, the future of robotic surgery appears promising, given the emergence of new technologies and the enhancement of training centers, which contribute to the strengthening and expansion of this field, including its application in general surgery.

Keywords: Robotic surgery, Minimally invasive surgery, Health technology assessment, General surgery, Cost-benefit analysis.

INTRODUCTION AND RATIONALE

The growth of robotic surgery, evident in the last two decades, signals an irreversible change in the paradigms of contemporary medicine, with the use of advanced technologies becoming increasingly intrinsic to surgical practices.[1] In this context, the use of this technology, which was initially restricted to specific areas, is now widespread across several specialties, including general surgery.[2]

The expansion of robotic technology, evident in university and reference hospitals, has enabled the enhancement of surgeons' skills, especially in procedures performed in restricted anatomical spaces. This approach allows for safer, more effective, and less invasive interventions.[1] Thus, the use of robots not only favors the surgeon's performance but also positively impacts the patient experience,

reducing recovery time and postoperative pain, in addition to providing better aesthetic outcomes.

However, the incorporation of this technology still faces barriers related to high cost, the need for highly specialized technical support, and the lack of structured training programs, which restricts its use to high-complexity medical centers with greater financial and human resources.[3]

On the other hand, despite these limitations, it is undeniable that surgical education in medical schools has been reconfigured. Gradually, more modern technologies have been safely and promisingly implemented, promoting effective learning and the development of a qualified workforce to operate robotic equipment with safety and precision.[4]

Furthermore, the outlook for this field is promising, with rapid technological evolution through the use of augmented reality, new platforms, and, more recently, artificial intelligence.[5] Thus, it is important to note that the emergence of new devices, cheaper, more precise, and more versatile, contributes to the dissemination and integration of these resources into medical practice, making this tool inseparable from contemporary surgical practice.

In this context, the aim of this integrative review is to gather and analyze recent scientific evidence on the incorporation of robotic surgery into general surgery, in order to provide a comprehensive and updated overview.

OBJECTIVES

This study aims to evaluate, through an integrative literature review, the incorporation of robotic surgery into general surgery practice, with emphasis on the identification of its main clinical, operational, and educational benefits, as well as the technical, structural, and economic challenges that still limit its widespread adoption. In addition, it seeks to analyze future perspectives for the use of this technology, considering the advancement of robotic platforms, the evolution of surgical training programs, and the impact of this modality on the quality of care and the training of new professionals.

METHODOLOGY

The methodology used to achieve the objective of this study, entitled "The Incorporation of Robotic Surgery into General Surgery Practice: Benefits, Challenges, and Future Perspectives", was the integrative literature review. According to Whittemore and Knafl[6] (The integrative review: updated methodology), the integrative review constitutes an approach that enables the synthesis of theoretical and empirical evidence on a specific topic, allowing for a broad and critical understanding of the phenomenon investigated. Thus, following this perspective, this study sought to integrate and analyze the available evidence in order to broaden the understanding of the benefits, challenges, and future perspectives of robotic surgery in general surgery practice.

To conduct this review, the methodological procedures described by Broome[7] were adopted, which involve the following steps: (a) identification of the problem and definition of the guiding question; (b) systematic search of studies in scientific databases; (c) application of inclusion and exclusion criteria; and (d) analysis and synthesis of the data obtained. The guiding question established was: "What are the benefits, challenges, and future perspectives of the incorporation of robotic surgery into general surgery practice?"

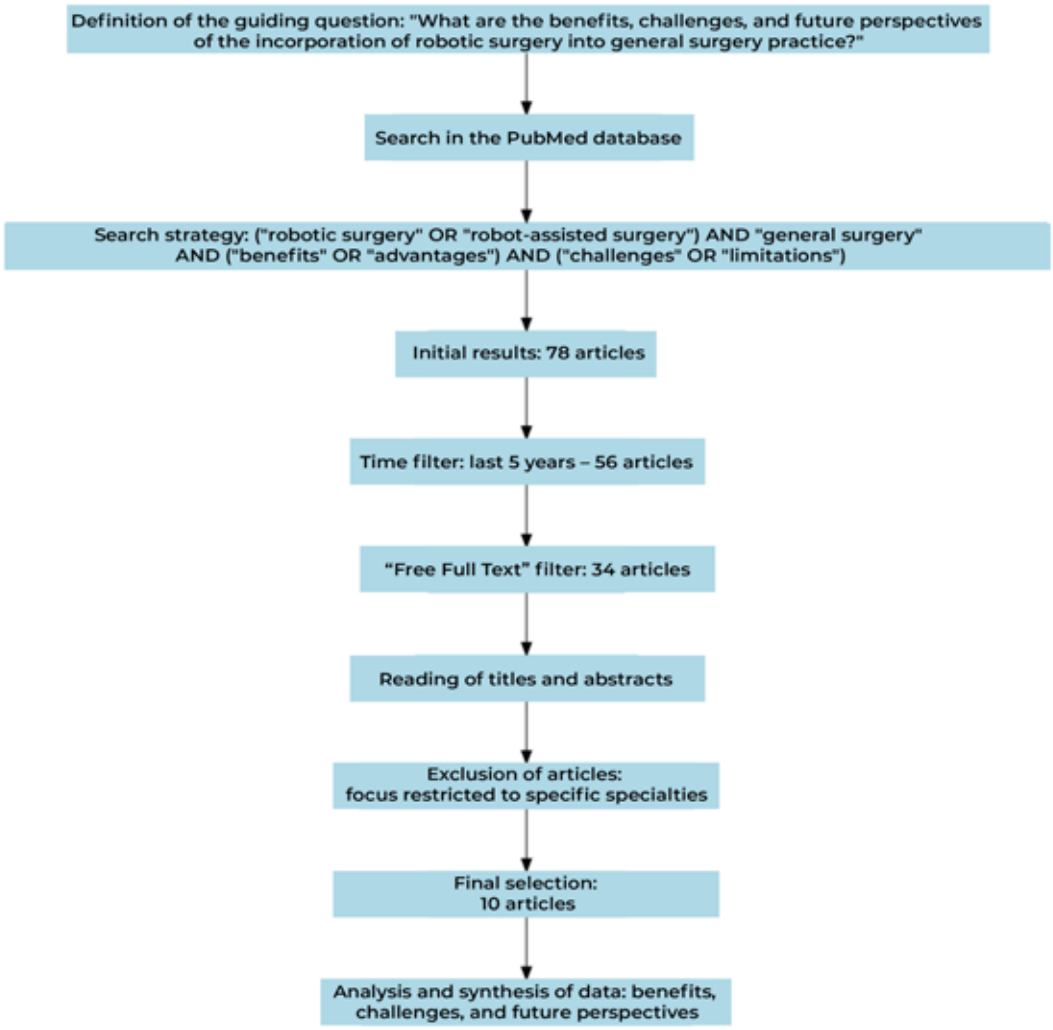
The search was carried out in the PubMed database using the following advanced search strategy: ("robotic surgery" OR "robot-assisted surgery") AND "general surgery" AND ("benefits" OR "advantages") AND ("challenges" OR "limitations"). Initially, 78 articles were found. Then, a time filter for the last five

years was applied, resulting in 56 articles. Subsequently, the “free full text” filter was used, yielding 34 full-text publications available.

After reading the titles and abstracts, inclusion and exclusion criteria were applied: articles published in English, available in full text, addressing robotic surgery broadly, with emphasis on its benefits, challenges, and future perspectives, within or in interface with general surgery, were included. Articles with a restricted focus on unrelated specialties were excluded. In the end, 10 articles were selected to compose this review.

The included studies addressed general aspects of robotic surgery and also discussed applications in related surgical specialties, such as gynecology and gastrointestinal procedures, providing a comprehensive view of the incorporation of this technology and its impact on contemporary surgical practice.

Table 1: Methodology for Article Selection



Source: Author’s elaboration, 2025

RESULTS AND DISCUSSION

The incorporation of robotic surgery into general surgery practice has promoted a profound transformation in contemporary operative paradigms. Over the past two decades, robotic platforms have evolved significantly and have increasingly been integrated into operating rooms, with particular emphasis on university hospitals and leading private institutions. What was once a technology restricted to niches such as urology and gynecology has expanded to encompass a much broader scope of procedures, including colorectal, esophagogastric, hepatobiliary, and even emergency interventions, consolidating robotic surgery as a versatile and promising tool.

From a technical standpoint, the main advantage of robotic surgery lies in its ability to enhance the surgeon's skills. Studies such as that of Gangemi et al.[5] demonstrate that the platform provides an enlarged three-dimensional high-definition view, combined with articulated instruments with seven degrees of freedom, allowing movements more precise and delicate than those obtained by conventional laparoscopy. In practice, this superiority translates into less tissue trauma, reduced intraoperative bleeding, lower risk of conversion to open surgery, and shorter hospital stay. These benefits are particularly evident in procedures performed in confined anatomical spaces, such as the deep pelvis, where millimetric precision in dissection has a direct impact on oncological and functional outcomes.

Cheng et al.[8], in reviewing the evolution of single-incision robotic-assisted surgery (SIRAS), highlight the technological effort to make procedures increasingly less invasive while maintaining safety and efficacy. The Da Vinci SP™ platform, for example, allows the entire procedure to be performed through a single port, using articulated instruments and a flexible endoscopic camera. The authors emphasize that this approach not only improves postoperative aesthetics but also reduces pain and recovery time. Figure 1, adapted from this study, illustrates the timeline marking the development of this technology,

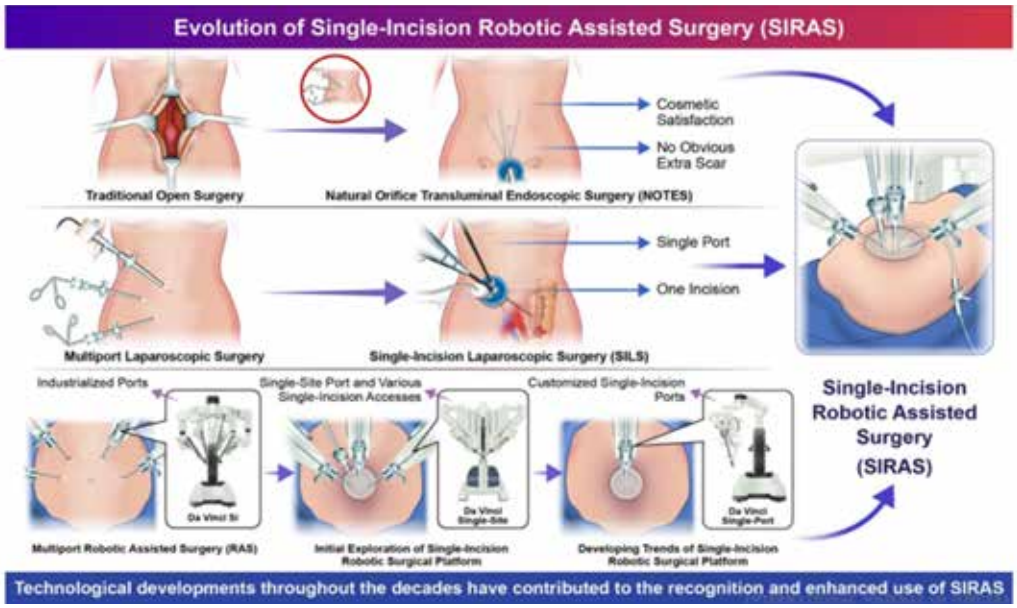


Figure 1. Timeline of the evolution of single-incision robotic surgery in general surgery (Adapted from Cheng et al., 2023, p. 4223).

In addition to technical benefits, robotics also contributes to surgeon ergonomics. As highlighted by Gangemi et al.[5], positioning at the robotic console, combined with the absence of direct contact with the patient and the elimination of physiological tremor, provides a more comfortable and less exhausting operative experience. This is particularly important in long or repetitive surgeries, in which physical fatigue can compromise the surgeon's performance and the safety of the procedure. This paradigm shift also positively influences the occupational health of professionals, reducing the incidence of musculoskeletal injuries associated with traditional surgical practice.

Despite these advances, the large-scale adoption of robotic surgery still faces significant barriers. The most frequently cited in the literature concerns cost. According to Peng et al.[9], the investment required to acquire a robotic platform ranges from 1.5 to 2.5 million US dollars, in addition to recurring costs for maintenance, sterilization, instrument replacement, and training. Yadav et al.[10] specifically analyzed the economic impacts of robotic surgery in gynecology and observed that, although there are clear clinical advantages, hospital costs remain up to 30% higher compared to laparoscopy. This scenario limits the adoption of the technology to institutions with robust budgets, concentrating its use in large hospitals and deepening inequalities in access.

The financial impact is not limited to hospital infrastructure. As emphasized by Orvieto et al.[11], the adoption of robotics requires significant logistical changes, including new operative workflows, hiring of trained professionals, and adaptation of operating rooms. These adaptations not only increase indirect costs but also demand institutional maturation time for efficient program implementation. In addition, there are challenges related to the maintenance of the technology, which requires highly specialized technical support that is not always available in remote regions or peripheral centers.

Another central obstacle is the learning curve, pointed out as a limiting factor by several authors (Alverdy, Gangemi [12],[5]). Although the robotic console interface is intuitive, its mastery requires intensive practical training, generally in high-fidelity simulators, cadavers, or laboratory animals. The safe transition from simulated practice to the real clinical setting is gradual and must be accompanied by rigorous supervision, which demands time, investment, and standardized protocols. The absence of structured training programs in many countries compromises the training of new surgeons and may generate a false sense of security, increasing the risk of adverse events.

Population-based data on clinical outcomes also generate debate. Muaddi et al.[13], in a study with more than 100,000 robotic procedures performed in Canada, observed that although the rate of adverse events was lower than in open surgery, it was not statistically superior to laparoscopy in many interventions. This suggests that, for certain types of procedures, such as hysterectomies, cholecystectomies, and partial nephrectomies, the main benefit lies in the minimally invasive route itself and not necessarily in the platform used. Such findings reinforce the importance of well-established criteria for indication, avoiding trivialization of the technique and adoption driven by commercial pressures or unfounded expectations.

Despite these limitations, the prospects for robotic surgery are highly promising. The trend toward miniaturization of platforms, the development of independent robotic arms, the incorporation of artificial intelligence algorithms, and integration with real-time imaging point to a new generation of robots that are more accessible, precise, and versatile. Marchegiani et al.[14] describe the current clinical landscape of these platforms, while Peng et al.[9] highlight that new players in the market are breaking the previous monopoly, reducing costs through competition, and accelerating the pace of innovation. These new platforms, still in the stage of clinical trials, promise to expand accessibility and adapt to

different hospital realities, including small- and medium-sized hospitals.

In the field of medical training, a true reconfiguration of surgical education is observed. The combination of robotic simulators with augmented reality, libraries of operative videos, and collaborative learning platforms creates a favorable environment for active and safe learning. Gangemi et al.[5] emphasize that this immersive approach contributes to the training of a new generation of highly qualified surgeons, familiar with the latest technologies and prepared to integrate robotics into their daily practice.

In clinical terms, the trend is toward the expansion of robotics into more complex surgeries, such as major hepatic resections, pelvic exenterations, esophageal reconstructions, and emergency surgeries in patients with multiple comorbidities. Okamoto et al.[15] point out that, in Japan, there is increasing use of robotics in advanced reconstructive surgeries and in procedures with very narrow anatomical margins, where the precision of the robotic system becomes a critical differential for therapeutic success.

In view of this scenario, it is evident that robotic surgery, although still permeated by challenges, is on its way to becoming an inseparable part of modern surgical practice. Its incorporation, when carried out in a judicious, ethical, and evidence-based manner, has the potential to raise the standard of surgical care, benefit patients and professionals, and redefine the boundaries of general surgery for the coming decades.

CONCLUSION

Based on the results presented, it is concluded that robotic surgery is a promising tool in different areas of intervention, due to its ability to provide the surgeon with more precise movements, thereby causing less tissue trauma. However, as it is still a relatively recent resource, there are challenges to be overcome in its use, such as the high cost of the technology, the materials used, and, consequently, the procedure itself.

In this sense, further studies are needed to compare the cost-effectiveness of robot-assisted surgeries, laparoscopic surgeries, and open surgeries, fully assessing the panorama of costs, intraoperative and postoperative complications, readmissions, length of hospital stay and recovery, mortality, among other relevant factors. In this way, it will be possible to establish more specific eligibility criteria for robotic surgeries, while, for now, the surgical approach is defined by technical feasibility and the surgeon's assessment.

In addition, there is a need to review training in robotic surgery and regulatory policies for the use of robotic platforms, since there is no general consensus for assessing the surgeon's competence in this modality, which has its own specificities regarding handling and technique.

Thus, the benefits of robotic surgery in daily hospital practice are noteworthy, but in order for the technology to be used in the best possible way, further studies and discussions on the subject are still required.

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EDITORIAL AND REVIEW

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SCIENTIFIC ARTICLE - INTEGRATIVE REVIEW

IMMUNE-MEDIATED RHEUMATIC DISEASES AND THEIR PERIPHERAL NEUROPATHY MANIFESTATIONS

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ABSTRACT

Immune-mediated rheumatic diseases (IMRDs) frequently involve neurological complications, with peripheral neuropathy being a relevant but underdiagnosed manifestation. This integrative review evaluated evidence on the prevalence, clinical patterns, and associated factors of neuropathy in rheumatoid arthritis, Sjögren's disease, systemic lupus erythematosus, and systemic vasculitis. A literature search was conducted in the PubMed database, including studies published between 2010 and 2025. Findings show that peripheral neuropathy is highly prevalent in rheumatoid arthritis, often subclinical, and in vasculitis, where it presents acutely and with severe symptoms. In Sjögren's disease, specific sensory forms and small fiber neuropathy may precede classic symptoms. In systemic lupus erythematosus, neuropathy occurs early and in association with disease activity and responds well to immunosuppressive therapy. The study highlights the importance of early identification of peripheral neuropathy in autoimmune diseases, allowing more effective interventions and improved functional prognosis.

Keywords: Autoimmune diseases, Early diagnosis, Inflammation, Peripheral neuropathy, Rheumatology.

INTRODUCTION

Immune-mediated rheumatic diseases (IMRDs) comprise a group of chronic disorders characterized by dysregulation of the immune system, inflammation, and tissue destruction. Several systems and tissues are affected. Among the neurological manifestations, peripheral neuropathies stand out, as they may cause pain, paresthesia, loss of strength, and sensory or motor dysfunctions, leading to impaired quality of life. The rheumatic diseases with the highest prevalence of neuropathies are: rheumatoid arthritis (RA), Sjögren's disease (SD), systemic lupus erythematosus (SLE), and systemic vasculitides.[1]

Rheumatoid arthritis is a chronic inflammatory autoimmune disease that mainly affects small joints, leading to pain, stiffness, and joint deformities. In more advanced stages or in cases of high inflammatory activity, RA may present with extra-articular manifestations, including peripheral neuropathy. It is estimated that up to 75% of RA patients present some degree of neuropathy, even if subclinical. The most common manifestations include asymmetric sensorimotor neuropathy,

multiple mononeuropathy, and carpal tunnel syndrome.[2]

Sjögren's disease mainly affects exocrine glands, causing ocular and oral dryness, but it may also present significant extraglandular manifestations, such as joint, renal, pulmonary, and neurological involvement. Peripheral nervous system involvement in SD occurs in 15% of cases, and the most common forms are distal sensory axonal polyneuropathy and sensory neuronopathy (ganglionopathy), in addition to small fiber neuropathy — often associated with severe pain and autonomic dysfunction. In many cases, neurological symptoms precede the clinical diagnosis of SD, hindering early identification of the disease.[3]

Systemic lupus erythematosus is a multisystemic autoimmune inflammatory disease characterized by the production of autoantibodies and immune complex formation, with the potential to compromise any organ, including the nervous system. Peripheral neuropathy in SLE is frequently associated with inflammatory disease activity, and the most commonly observed forms are axonal sensorimotor polyneuropathy, multiple mononeuropathy, and, more rarely, cranial neuropathies. The pathogenic mechanisms include peripheral vasculitis, immune complex deposition, and immune-mediated neuronal damage.[4]

Systemic vasculitides comprise a heterogeneous group of diseases characterized by inflammation of blood vessels, which may affect arteries, venules, and capillaries of different calibers. When the vasa nervorum is involved, ischemia and tissue necrosis may occur, leading to the development of multiple mononeuropathy, the most common clinical form of vasculitic neuropathy. Vasculitides such as polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and cryoglobulinemic vasculitis are most frequently associated with this type of involvement.[5],[6]

Although pathophysiological mechanisms may vary and clinical manifestations may be similar, there are specific forms of neuropathy in each condition: sensory neuronopathy and small fiber neuropathy in SD; sensorimotor axonal patterns in SLE; carpal tunnel syndrome and subclinical neuropathy in RA; and painful multiple mononeuropathy in vasculitides. Recognizing the different clinical presentations of neuropathy in patients with IMRDs is essential for treatment, providing these patients with better quality of life. This review aims to analyze peripheral neuropathies observed in IMRDs (rheumatoid arthritis, Sjögren's disease, systemic lupus erythematosus, and vasculitis), considering their main clinical, diagnostic, and associated aspects.

METHOD

This study is an integrative literature review, aimed at gathering and critically analyzing the available evidence on the occurrence of peripheral neuropathies in immune-mediated rheumatic diseases.

Data collection was carried out through a search in the PubMed database, between May and July 2025. The search strategy involved combining the descriptor "peripheral neuropathy" with the English names of the following autoimmune diseases: systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and systemic vasculitis. Thus, four independent searches were performed, using the following pairs of descriptors: "peripheral neuropathy" AND "systemic lupus erythematosus," "peripheral neuropathy" AND "Sjögren's syndrome," "peripheral neuropathy" AND "rheumatoid arthritis," and "peripheral neuropathy" AND "systemic vasculitis." Finally, a fifth independent search was conducted combining the descriptors "peripheral neuropathy" AND "rheumatic diseases," in order to cover the broader theme.

In each of these searches, only articles that contained both descriptors in the title were selected, ensuring that peripheral neuropathy was directly related to the autoimmune disease investigated. A temporal filter was also applied, including only publications from the last 15 years (2010 to 2025), in order to guarantee the timeliness of the evidence analyzed.

Article screening was carried out based on the reading of titles and abstracts, considering relevance to the topic. Studies considered relevant were then evaluated in full. Original articles, systematic reviews, and narrative reviews published in English, Portuguese, or Spanish were included. Duplicate articles, those without access to the full text, or those addressing non-peripheral neurological manifestations were excluded.

Each set of studies, corresponding to one of the autoimmune diseases investigated, was analyzed separately. The selected articles were evaluated based on their scientific relevance and methodological quality. The extracted information included: type of peripheral neuropathy described, frequency, clinical presentation, diagnostic methods, pathophysiological mechanisms, and therapeutic approaches.

The results were organized descriptively, by autoimmune disease, to allow a clear comparison between the findings of each group.

DISCUSSIONS

The main results of the articles included in this review are presented in Table 1:

Table 1. Main results of the selected articles

Titles	Authors/Year	Main results
Clinical characteristics of rheumatoid arthritis patients with peripheral neuropathy and potential related risk factors.	Li et al.[2]	Prevalence of PN: 50%; Types: 63.6% sensorimotor, 18.2% pure sensory, 13.6% pure motor; 22.7% with carpal tunnel syndrome; Risk factors: total protein < 63 g/L, anti-CCP < 285.7 U/mL, elevated CRP and platelets in severe cases; High association with neurological symptoms and loss of reflexes.

Prevalence and patterns of peripheral neuropathy in patients of rheumatoid arthritis.	Kaeley et al.[7]	Prevalence of PN: 75.3%; 50.7% with subclinical neuropathy; Types: 33.7% sensorimotor, 22.4% pure motor, 8.9% multiple mononeuropathy, 8.9% compressive; Association with age, longer disease duration, higher DAS-28, ESR and CRP; Worse functionality (HAQ-DI) and greater pain (VAS) in patients with PN.
Primary Sjögren syndrome-related peripheral neuropathy: A systematic review and meta-analysis.	Liampas et al.[8]	Prevalence of PN: 15% (in >5,600 patients); Most common type: distal axonal polyneuropathy (80%); Second most common form: sensory neuronopathy (20%); Mononeuropathy (e.g., carpal tunnel) in 12.8%; Trigeminal neuropathy in 3.9%; Associated factors: advanced age and vasculitis; Neurological symptoms often precede the diagnosis of SD.
Relation of Sensory Peripheral Neuropathy in Sjögren Syndrome to Anti-Ro/SSA.	Scofield et al.[9]	31% of patients with SD presented sensory peripheral neuropathy; Significant association with anti-Ro/SSA and anti-La/SSB detected by immunodiffusion (66.7% of those with both antibodies had PN); Isolated anti-Ro: 48.1% with PN; No significant association with vitamin B12; More sensitive

		techniques (ELISA, BioPlex) showed no correlation with PN.
Peripheral Neuropathy in Patients with Systemic Lupus Erythematosus.	Florica et al.[4]	Prevalence of PN: 13.5%; 60.3% of cases attributed to SLE; Most common forms: sensory or sensorimotor polyneuropathy, multiple mononeuropathy, cranial neuropathy; Predominance of asymmetric and distal involvement; 74% with axonal pattern on electroneuromyography; SLEDAI significantly higher in cases attributed to SLE; Favorable therapeutic response in 66% of cases.
Short- and Long-Term Outcome of Systemic Lupus Erythematosus Peripheral Neuropathy: Bimodal Pattern of Onset and Treatment Response.	Fargetti et al.[10]	Prevalence of PN attributed exclusively to SLE: 1.8%; Most cases occur within the first 5 years of disease; Most common type: axonal sensorimotor polyneuropathy (71.1%); Main symptoms: paresthesia, pain, weakness, gait disturbance; 92.1% with clinical improvement after 1 year; 89.3% in remission after 5 years; High frequency of immunosuppressant and corticosteroid use.
Neuropathy associated	Graf and Imboden[5]	Frequency of PN: PAN

with vasculitis.		(85%), EGPA (60–80%), MPA (40–50%), GPA (20–25%); Predominant clinical form: painful and asymmetric multiple mononeuropathy; Most affected nerves: deep fibular, ulnar; Nonsystemic vasculitic neuropathy (NSVN) in 25% of cases; Histological lesions: fibrinoid necrosis, transmural infiltrate, and vascular occlusion.
Peripheral neuropathy in systemic vasculitis and other autoimmune diseases – a report of five cases.	Rodrigues et al.[11]	Study of 5 cases with PN due to systemic vasculitis: MPA, HBV-PAN, EGPA, and an undetermined case; Pattern: asymmetric sensorimotor axonal neuropathy; Progression to multiple mononeuropathy with overlapping pattern; Diagnosis confirmed by nerve/skin biopsy; Treatment with corticosteroid, cyclophosphamide, and antivirals; Good clinical response and variable prognosis.

Source: authors' elaboration.

This integrative literature review highlighted peripheral neuropathy as a relevant manifestation in several immune-mediated rheumatic diseases (IMRDs), with clinical, pathophysiological, and therapeutic characteristics that vary according to the underlying etiology. The results obtained from the analysis of the selected studies identified patterns of prevalence, clinical presentations, risk factors, and outcomes associated with PN in the IMRDs evaluated: rheumatoid arthritis (RA), Sjögren's disease (SD), systemic lupus erythematosus (SLE), and systemic vasculitis. The high frequency and heterogeneity of PN hinder its detection and clinical management in these conditions.

1. Rheumatoid Arthritis

In rheumatoid arthritis, PN proved to be highly prevalent, identified in about 75.3% of patients in Kaeley et al.[7] and in 50% in the study by Li et al.[2] An interesting finding of Kaeley et al.[7] is that, among the affected patients, approximately half of the PN cases were subclinical, asymptomatic on

neurological clinical evaluation, requiring complementary tests, such as electroneuromyography, for detection. The most frequently observed clinical patterns in these studies were asymmetric axonal sensorimotor neuropathies, multiple mononeuropathy, carpal tunnel syndrome, and pure motor neuropathy. This diversity of clinical manifestations in RA suggests different mechanisms, including mechanical compression (as in carpal tunnel syndrome), systemic inflammatory activity, and neural damage secondary to the progression of joint disease.

In the study by Li et al.[2], among the 44 patients with PN, 28 presented multiple nerve involvement (11 with polyneuropathy and 17 with multiple mononeuropathy) and 16 presented single nerve involvement (10 with carpal tunnel syndrome). In cases with symptoms, the most frequent were numbness (97.7%), pain (54.5%), paresthesia (45.5%), and weakness (36.4%). Objective findings included loss of deep reflexes (84%), especially in knees and ankles, and sensory alterations such as decreased analgesia (65.9%), apselaphesia (61.3%), and thermesthesia (40.9%).

Neurological involvement was also correlated with longer RA duration, higher inflammatory disease activity (elevated CRP and DAS-28), presence of joint erosions, subcutaneous nodules, and muscle atrophy. In addition, these patients presented higher scores of functional disability (HAQ-DI) and greater pain intensity (VAS). Laboratory tests showed relevant inflammatory and immunological alterations in patients with PN compared to others, such as hypoalbuminemia, thrombocytosis, leukocytosis, and low anti-CCP levels, especially in more severe cases. These findings support the relationship between chronic inflammation and peripheral neurological involvement in RA.

2. Sjögren's Disease

In Sjögren's disease, peripheral neuropathy is one of the main extraglandular manifestations, with a prevalence of approximately 15%, according to the meta-analysis by Liampas et al.[8] In contrast to RA, in which neuropathy is generally silent, in pSS neuropathic symptoms, when present, are evident and may even precede the diagnosis of the disease. These include burning pain, allodynia, hypoesthesia, tingling, loss of balance, and muscle weakness. Pain tends to worsen at night and can be disabling. Motor involvement, although less common, is also reported in more severe cases. The most frequent clinical form is distal axonal polyneuropathy (80%), length-dependent, usually painful, with paresthesia, allodynia, and hypoesthesia, especially in the lower limbs. Next, sensory neuronopathy (20%) stands out, presenting asymmetry and not length-dependence, with sensory ataxia and sometimes cerebellar involvement. Less frequent forms include multiple mononeuropathy, pure motor neuropathies, and polyradiculoneuropathies.

Regarding the presence of small fiber neuropathies (SFN), associated with burning pain, pruritus, autonomic dysfunction, and allodynia, few studies have investigated their occurrence in SD using different diagnostic approaches. According to Liampas et al.[8], the prevalence of pure SFN in patients with SD was 9.2% in the only study that followed well-established criteria. Its manifestation is associated with a higher prevalence of restless legs syndrome and also with reduced electrochemical conductance of the skin, revealing possible concomitant involvement of both large and small nerve fibers. This neuropathy is difficult to study due to the challenges in its diagnosis, which is established by determining small fiber density in a skin biopsy, as reported by Scofield et al.[9], since electroneuromyography is normal in these cases.

Peripheral mononeuropathies have also been observed in SD, such as carpal tunnel syndrome, with a prevalence of 12.8%, and cranial neuropathies, mainly of the trigeminal nerve, which affect 3.9% of

patients with SS, possibly related to a generalized ganglionopathy.[8]

The results of the study by Scofield et al.[9] revealed a significant association between certain immunological factors and the occurrence of peripheral sensory neuropathy in patients with SD, suggesting a possible pathogenic role of these markers. The frequency of neuropathy was substantially higher (66.7%) among individuals with anti-Ro (SSA) and anti-La (SSB) autoantibodies detected by immunodiffusion, compared to only 25% in those without these antibodies ($p = 0.0036$). Furthermore, even the isolated presence of anti-Ro was significantly associated with neuropathy (48.1% versus 23%, $p = 0.018$). These findings reinforce the clinical relevance of identifying these autoantibodies in the context of correlating them with neuropathic involvement, particularly when assessed by immunodiffusion. However, more sensitive methods, such as ELISA and BioPlex, did not show a significant correlation with neuropathy, which may indicate differences in the specificity of the methods or in the detection of distinct autoantibody subpopulations. This suggests the need for standardization and caution in the interpretation of serological tests when evaluating neuropathies, although they should certainly be taken into account due to their aforementioned relevance.

The study also excluded any association between serum vitamin B12 levels and the presence of neuropathy in SD, suggesting that this is not a relevant factor in this context.

3. Systemic Lupus Erythematosus

In systemic lupus erythematosus, there was relevant variation in the prevalence of PN among the studies analyzed, due to the difficult characterization stemming from the diversity of clinical presentations and the multiplicity of possible causes. While Florica et al.[4] reported 13.5%, Fargetti et al.[10], using more restrictive exclusion criteria and electrophysiological confirmation, considering only cases attributed exclusively to SLE, reported only 1.8%. Most cases manifested within the first five years of the disease, with an emphasis on early-onset cases (36.6%) (within the first year), which showed high inflammatory activity (SLEDAI = 21.3) compared to late-onset cases (SLEDAI = 3.9). The most commonly observed pattern was axonal sensorimotor polyneuropathy, but there were also reports of mononeuropathies, polyradiculoneuropathy, and cranial neuropathy.

Regarding symptoms, the most frequently reported were paresthesia (81.6%), pain (57.9%), muscle weakness (52.6%), and gait disturbances (42.1%). All patients presented lower limb involvement, and about one-third (31.5%) also showed upper limb involvement. Electroneuromyography revealed a predominance of axonal lesions, with mixed or demyelinating patterns in some cases. Regarding therapy, all patients received corticosteroid treatment, with dose escalation (76.3%) and pulse therapy (55.2%) required in most cases. Immunosuppressants were initiated in 97.3% of patients, particularly intravenous cyclophosphamide (50%) and azathioprine (42.1%). There was a high treatment response, with complete or partial clinical remission after one year in the majority of cases (92.1%), and maintenance of this response after five years, with 89.3% still in remission. These findings demonstrate the potential reversibility of neuropathic involvement in SLE, provided that there is early recognition and adequate treatment.

The Canadian study by Florica et al.[4] evaluated 207 patients with PN among 1,533 patients with SLE, with 60.3% of PN cases attributed to SLE. The most common clinical form was sensory or sensorimotor polyneuropathy, with a predilection for distal and asymmetric involvement (59%), mainly of the sural, fibular, median, and ulnar nerves. Less common forms included multiple mononeuropathy (9.2%), cranial neuropathy (12.5%), CIDP (5.3%), and AIDP (1%). Electroneuromyography showed axonal neuropathy in

74% of patients with PN attributed to SLE.

Patients with PN attributed to SLE presented higher disease activity (SLEDAI-2K = 11) compared with patients with PN from other causes (SLEDAI = 5). Multiple mononeuropathy was exclusive to cases attributed to SLE, reinforcing its association with active vasculitis. The most common treatment was oral corticosteroids or pulse therapy, with a favorable clinical response in about 66% of patients.

Both studies reinforce that PN in SLE may arise at different stages of the disease and is frequently associated with systemic inflammatory activity, especially when onset is early. Immunological markers associated with PN include lymphopenia, cutaneous vasculitis, and anti-Sm positivity, particularly in the Brazilian study.

4. Systemic Vasculitides

In systemic vasculitides, peripheral neuropathy is observed as one of the most prevalent and striking manifestations, particularly in polyarteritis nodosa (PAN), ANCA-associated vasculitis (granulomatosis with polyangiitis – GPA, microscopic polyangiitis – MPA, and eosinophilic granulomatosis with polyangiitis – EGPA), and cryoglobulinemic vasculitis associated with HCV. Vasculitic neuropathy may also occur in a form limited to the peripheral nervous system, called nonsystemic vasculitic neuropathy (NSVN). Graf and Imboden[5] described PN in up to 85% of patients with PAN, 60–80% in EGPA, 40–50% in MPA, and 20–25% in GPA. The most dominant form is multiple mononeuropathy, with asymmetric, acute or subacute, painful involvement, especially of lower limb nerves such as the deep fibular (causing foot drop) and upper limb nerves such as the ulnar. Pathophysiologically, there is involvement of transmural inflammation of the vasa nervorum with fibrinoid necrosis, perivascular infiltration, and vascular occlusion. In cases of NSVN, the inflammatory process is restricted to the peripheral nerve, often without systemic symptoms, making diagnosis difficult. It is estimated that 25% of vasculitic neuropathies are NSVN, with a more insidious and progressive presentation and a less aggressive course.

The study by Rodrigues et al.[11] detailed clinical cases of vasculitic neuropathy, including HBV-associated PAN, MPA, EGPA, and vasculitis without specific definition. Most patients presented progressive asymmetric sensorimotor deficits, characterizing multiple mononeuropathy evolving into distal asymmetric polyneuropathy. In all cases, electroneuromyography revealed an asymmetric axonal pattern, with skin or nerve biopsy being fundamental for diagnostic confirmation. Typical histological findings included asymmetric loss of nerve fibers, perivascular inflammatory infiltrate, fibrinoid necrosis, and signs of vascular recanalization. The presence of constitutional symptoms (weight loss, low-grade fever, asthenia), skin lesions, and systemic signs aided in etiological differentiation. Regarding treatment, corticosteroid therapy with immunosuppressants (cyclophosphamide or azathioprine) was used, in addition to antivirals in HBV-associated vasculitis. Clinical response was favorable in most patients, with significant neurological recovery within weeks or months. The study reinforces the importance of early etiological characterization of PN, as therapeutic approaches vary according to the underlying vasculitis.

CONCLUSION

Peripheral neuropathies are frequent in IMRDs (rheumatoid arthritis, Sjögren's disease, systemic lupus erythematosus, and systemic vasculitis), and even with differences in the pathophysiology of each disease, they present certain similarities, with varying degrees of pain, paresthesia, weakness, and sensory or motor dysfunctions. Subclinical presentation may occur in rheumatoid arthritis, which suggests investigation even in oligosymptomatic patients. In SD, neuropathy may precede sicca

symptoms, in which case the investigation of anti-Ro antibodies is important for suspicion. In SD, small fiber neuropathy also stands out, which is difficult to diagnose, with normal electroneuromyography, requiring skin biopsy. In systemic lupus erythematosus, PN occurs early, associated with high inflammatory activity, with good prognosis when treated promptly. Finally, in systemic vasculitides, multiple mononeuropathy is the most common and severe form, with biopsy being essential for diagnosis and therapeutic response generally favorable. The recognition and diagnosis of neuropathy in IMRDs are essential for early treatment and improved quality of life for patients.

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EDITORIAL AND REVIEW

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