

USE OF BOTULINUM TOXIN AS A THERAPEUTIC APPROACH FOR SIALORRHEA IN CRITICALLY ILL PATIENTS: A SYSTEMATIC REVIEW

USO DA TOXINA BOTULÍNICA COMO ABORDAGEM TERAPÊUTICA PARA A
SIALORREIA EM PACIENTES EM ESTADO CRÍTICO: UMA REVISÃO
SISTEMÁTICA

USO DE LA TOXINA BOTULÍNICA COMO ENFOQUE TERAPÉUTICO PARA
LA SIALORREA EN PACIENTES EN ESTADO CRÍTICO: UNA REVISIÓN
SISTEMÁTICA

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ABSTRACT

Introduction: Sialorrhea may increase the risk of aspiration and respiratory complications in critically ill patients. Botulinum toxin type A is a safe and effective treatment option, supporting its potential use in intensive care. Objective: To evaluate the effectiveness of botulinum toxin as a therapeutic option for the management of sialorrhea in critically ill patients. Methods: A systematic review was conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* guidelines. Electronic searches were performed in PubMed, Google Scholar, SciELO, Web of Science, Cochrane Library, ScienceDirect, and OpenGrey. Randomized clinical trials evaluating botulinum toxin for the treatment of sialorrhea were included. Seven studies met the eligibility criteria and were analyzed. The review was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42023452585), and the risk of bias was assessed using the Cochrane Risk of Bias tool.

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Results: The included studies consistently demonstrated that botulinum toxin reduced salivary flow and effectively controlled sialorrhea in patients with neurological disorders and other conditions associated with excessive salivation. Ultrasound-guided injection was the most frequently reported technique, contributing to greater accuracy and safety. Most studies presented a low risk of bias, supporting the reliability of the available evidence. **Conclusion:** Current evidence suggests that botulinum toxin is a safe and effective therapeutic option for managing sialorrhea. Its use may improve oral health care and support multidisciplinary management of critically ill patients, particularly when applied using standardized injection protocols.

Keywords: Botulinum Toxins. Sialorrhea. Critical Illness. Intensive Care Units. Dentistry. Salivary Glands.

RESUMO

Introdução: A sialorreia pode aumentar o risco de aspiração e complicações respiratórias em pacientes criticamente enfermos. A toxina botulínica tipo A é uma opção de tratamento segura e eficaz, destacando seu potencial uso em unidades de terapia intensiva. **Objetivo:** Avaliar a eficácia da toxina botulínica como opção terapêutica para o tratamento da sialorreia em pacientes em estado crítico. **Métodos:** Foi realizada uma revisão sistemática de acordo com as diretrizes do Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). As buscas eletrônicas foram realizadas no PubMed, Google Scholar, SciELO, Web of Science, Cochrane Library, ScienceDirect e OpenGrey. Foram incluídos ensaios clínicos randomizados que avaliaram a toxina botulínica para o tratamento da sialorreia. Sete estudos atenderam aos critérios de elegibilidade e foram analisados. A revisão foi registrada prospectivamente no International Prospective Register of Systematic Reviews (CRD42023452585), e o risco de viés foi avaliado utilizando a ferramenta Cochrane Risk of Bias. **Resultados:** Os estudos incluídos demonstraram consistentemente que a toxina botulínica reduziu o fluxo salivar e controlou eficazmente a sialorreia em pacientes com distúrbios neurológicos e outras condições associadas à salivagem excessiva. A injeção guiada por ultrassom foi a técnica mais frequentemente relatada, contribuindo para maior precisão e segurança. A maioria dos estudos apresentou baixo risco de viés, corroborando a confiabilidade das evidências disponíveis. **Conclusão:** As evidências atuais sugerem que a toxina botulínica é uma opção terapêutica segura e eficaz para o tratamento da sialorreia. Seu uso pode melhorar os cuidados com a saúde bucal e contribuir para o tratamento multidisciplinar de pacientes em estado crítico, especialmente quando aplicada seguindo protocolos padronizados de injeção.

Palavras-chave: Toxinas Botulínicas. Sialorreia. Doença Grave. Unidades de Terapia Intensiva. Odontologia. Glândulas Salivares.

RESUMEN

Introducción: La sialorrea puede aumentar el riesgo de aspiración y complicaciones respiratorias en pacientes críticamente enfermos. La toxina botulínica tipo A es una opción de tratamiento segura y eficaz, lo que respalda su potencial uso en unidades de cuidados intensivos. **Objetivo:** Evaluar la eficacia de la toxina botulínica como opción terapéutica para el tratamiento de la sialorrea en pacientes en estado crítico. **Métodos:** Se llevó a cabo una revisión sistemática siguiendo las directrices de los «Preferred Reporting Items for Systematic Reviews and Meta-Analyses» (PRISMA). Se realizaron búsquedas electrónicas en PubMed, Google Scholar,

SciELO, Web of Science, Cochrane Library, ScienceDirect y OpenGrey. Se incluyeron ensayos clínicos aleatorizados que evaluaban la toxina botulínica para el tratamiento de la sialorrea. Siete estudios cumplieron los criterios de elegibilidad y fueron analizados. La revisión se registró de forma prospectiva en el Registro Internacional Prospectivo de Revisiones Sistemáticas (CRD42023452585), y el riesgo de sesgo se evaluó mediante la herramienta Cochrane de evaluación del riesgo de sesgo. Resultados: Los estudios incluidos demostraron de forma sistemática que la toxina botulínica reducía el flujo salival y controlaba eficazmente la sialorrea en pacientes con trastornos neurológicos y otras afecciones asociadas a una salivación excesiva. La inyección guiada por ecografía fue la técnica más frecuentemente descrita, lo que contribuyó a una mayor precisión y seguridad. La mayoría de los estudios presentaron un bajo riesgo de sesgo, lo que respalda la fiabilidad de la evidencia disponible. Conclusión: La evidencia actual sugiere que la toxina botulínica es una opción terapéutica segura y eficaz para el tratamiento de la sialorrea. Su uso puede mejorar la atención de la salud bucodental y contribuir al tratamiento multidisciplinar de pacientes en estado crítico, especialmente cuando se aplica siguiendo protocolos estandarizados.

Palabras clave: Toxinas Botulínicas. Sialorrea. Enfermedades Graves. Unidades de Cuidados Intensivos. Odontología. Glándulas Salivales.



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INTRODUÇÃO

Botulinum toxin (BTX) is a neurotoxin produced by the Gram-positive, rod-shaped, spore-forming, motile, anaerobic bacterium *Clostridium botulinum* (Awan, 2017). Its structure consists of 1,295 amino acids, and its active component has a molecular weight of approximately 150 kilodaltons (kDa), comprising one heavy chain and one light chain linked by a single disulfide bond (Petracca *et al.*, 2015).

The therapeutic development of BTX began in the 1960s as an alternative treatment for strabismus through the work of ophthalmologist Alan B. Scott at the Smith-Kettlewell Eye Research Institute, California, United States (Barbosa; Barbosa, 2017). In Brazil, its clinical use was approved by the National Health Surveillance Agency (ANVISA) and the Ministry of Health in 1992. However, its use became widespread in 2000, when ANVISA authorized the commercialization of the first botulinum toxin product, BOTOX® (Francescon, 2014).

Seven serotypes of botulinum toxin have been identified (A, B, C1, D, E, F, and G), with serotype A (BTX-A) being the most commonly used for therapeutic applications in dentistry. The commercial name "Botox" is commonly used to refer to this subtype A neurotoxina

(Machado, 2023).⁽⁵⁾ Following injection, botulinum toxin inhibits the release of the neurotransmitter acetylcholine at cholinergic nerve terminals, thereby preventing muscle contraction. Its effects are dose-dependent, rapid, and reversible because of gradual neuronal regeneration, making repeated applications necessary after the pharmacological effects subside (Awan, 2017; Marciano *et al.*, 2014).

In dentistry, botulinum toxin has been widely used in orofacial harmonization and has emerged as a valuable therapeutic tool for the management of several disorders affecting the stomatognathic system (Pedron, 2015). The use of botulinum toxin type A for the treatment of sialorrhea has proven to be both effective and safe, with a low incidence of adverse effects. These findings support its therapeutic application in intensive care units, highlighting its potential role in preventing aspiration and reducing the risk of severe complications, such as hospital-acquired pneumonia (Pedron, 2015).

The Intensive Care Unit (ICU) is primarily dedicated to the stabilization and management of critically ill patients. In recent years, increasing attention has been given to interventions that may improve patient recovery and quality of life. The therapeutic use of botulinum toxin may contribute to better clinical outcomes by facilitating both medical and dental care, thereby supporting a more effective recovery process. However, the decision to administer botulinum toxin in the maxillofacial region of critically ill patients should be carefully evaluated and supervised by a specialized multidisciplinary team, considering the risks and benefits of each individual case (Woinarovicz; Moreira, 2020).

Sialorrhea is a condition commonly observed in individuals with cerebral palsy, Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, stroke, and other degenerative neurological disorders (Hockstein *et al.*, 2004). Aspiration of saliva, as well as other oral contents, may lead to serious respiratory complications (Hockstein *et al.*, 2004). In addition, sialorrhea is associated with facial skin irritation, unpleasant odor, increased oral and perioral infections, impaired oral hygiene, and dehydration (Hockstein *et al.*, 2004). These complications, together with dermatitis, social isolation, and psychological distress, contribute to a substantial reduction in patients' quality of life (Corso *et al.*, 2011).

Botulinum toxins are believed to reduce salivary secretion by inhibiting the release of acetylcholine from parasympathetic autonomic and postganglionic sympathetic cholinergic nerve terminals that innervate the salivary glands. The parotid, submandibular, and sublingual glands together produce nearly all saliva (Ondo; Hunter; Moore, 2004). Therefore,

intraglandular injection of botulinum neurotoxin type A (BTX-A) has become the first-line treatment for sialorrhea (Bekkers *et al.*, 2020).

For this reason, it is essential that dentists involved in the care of critically ill patients have a thorough understanding of sialorrhea and the therapeutic use of botulinum toxin, including salivary gland anatomy, appropriate dosing, and injection techniques. Such knowledge enables more effective participation in the multidisciplinary team and contributes to improved oral health and overall patient care (Moisés, 2021).

METHODS

Study Design

This study is a systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023452585. The review followed six methodological stages: identification of the research topic and formulation of the research question; establishment of inclusion and exclusion criteria; definition of the data to be extracted from the selected studies; critical appraisal of the included studies; data analysis; and synthesis and presentation of the findings (Souza *et al.*, 2022).

The research question was: "Is the therapeutic use of botulinum toxin effective for the treatment of sialorrhea in critically ill patients?" The question was developed using the PICO framework, in which P represents the population (critically ill patients), I the phenomenon of interest (treatment of sialorrhea), and Co the context (quality of life).

A comprehensive literature search was conducted between August 2023 and August 2024 in the following electronic databases: MEDLINE/PubMed, Web of Science, Cochrane Library, ScienceDirect, OpenGrey, Google Scholar, and the Scientific Electronic Library Online (SciELO). The search strategies used for each database are presented in Table 1.

Table 1

Search strategies used for each database.

Database	Keywords
PubMed	("Intensive care unit OR Intensive Care Unit OR Unit, Intensive Care ICU Intensive Care Units") AND (SIALORRHEA) AND ("Botulinum Toxins[Mesh]") Botulinum Toxins/therapeutic use [Mesh] OR (Toxins, Botulinum OR Botulinum Neurotoxins OR Neurotoxins, Botulinum OR Botulinum Toxin OR Toxin, Botulinum OR Clostridium botulinum Toxins OR Toxins Clostridium botulinum OR Botulinum Neurotoxin OR Neurotoxin, Botulinum OR Botulin) AND (head OR heads) AND (Neck OR necks) AND (Acetylcholine Release Inhibitors OR Inhibitors, Acetylcholine Release Acetylcholine Release Antagonists OR Antagonists, Acetylcholine Release OR Acetylcholine Release Blockers OR Blockers, Acetylcholine Release OR Release Blockers, Acetylcholine)
Web Of Science	(ALL=(Botulinum Toxins)) AND (QMTS=("Intensive care unit"))
Cochrane	'Botulinum Toxins' AND 'Intensive care unit'
SciELO	"Botulinum Toxins" AND "Head OR heads" AND "Neck OR Necks" AND "Intensive Care Unit"
Open Gray	"Botulinum Toxins" AND "Head OR heads" AND "Neck OR Necks" AND "Intensive Care Unit"
Google Scholar	(Botulinum Toxins[Mesh]) Botulinum Toxins/therapeutic use [Mesh] OR (Toxins, Botulinum OR Botulinum Neurotoxins OR Neurotoxins, Botulinum OR Botulinum Toxin OR Toxin, Botulinum OR Clostridium botulinum Toxins OR Toxins Clostridium botulinum OR Botulinum Neurotoxin OR Neurotoxin, Botulinum OR Botulin) AND (head OR heads) AND (Neck OR necks) AND (Acetylcholine Release Inhibitors OR Inhibitors, Acetylcholine Release Acetylcholine Release Antagonists OR Antagonists, Acetylcholine Release OR Acetylcholine Release Blockers OR Blockers, Acetylcholine Release OR Release Blockers, Acetylcholine)
Science Direct	Intensive care unit AND Botulinum Toxins AND (head OR neck) AND Acetylcholine Release Inhibitors

The inclusion criteria were: (a) articles addressing the use of botulinum toxin for the treatment of sialorrhea; and (b) randomized, double-blind, placebo-controlled clinical trials published in English, Spanish, and/or Portuguese. Monographs, dissertations, theses, books/book chapters, editorials, newspaper articles, integrative or systematic literature reviews, letters to the editor, reflective studies, experience reports, conference abstracts, website publications, and advertisements were excluded.

Study selection was performed using the Rayyan software, with independent duplicate data extraction by two reviewers, and was divided into two stages: screening of titles and

abstracts, followed by full-text assessment of the selected articles. In the first stage, two investigators independently screened the studies according to the inclusion and exclusion criteria, identifying potentially eligible studies and removing duplicates. In the second stage, the full texts of the selected articles were independently assessed. Any disagreements during the selection process were resolved by consulting a third independent reviewer to ensure the reliability and validity of the study.

During the data analysis stage, information was extracted from the included studies and summarized in a table containing the characteristics of the primary studies, including journal, title, authors/year, sample size, type of botulinum toxin, objectives, and the main findings related to the effectiveness of botulinum toxin in the treatment of sialorrhea.

After study selection, the risk of bias of the randomized clinical trials was assessed using the Cochrane Collaboration Risk of Bias (RoB 1.0) tool. This instrument evaluates seven main domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. For each domain, the risk of bias was classified as low risk, high risk, or unclear risk.

The required information was extracted directly from the full texts of the articles through a detailed assessment of the Methods and Results sections. Each domain was evaluated individually, and an overall risk of bias judgment was assigned to each study based on the classifications across all domains. The tool was applied in strict accordance with the guidelines provided in the *Cochrane Collaboration Handbook* for assessing risk of bias (Higgins *et al.*, 2011; Cochrane, 2008).

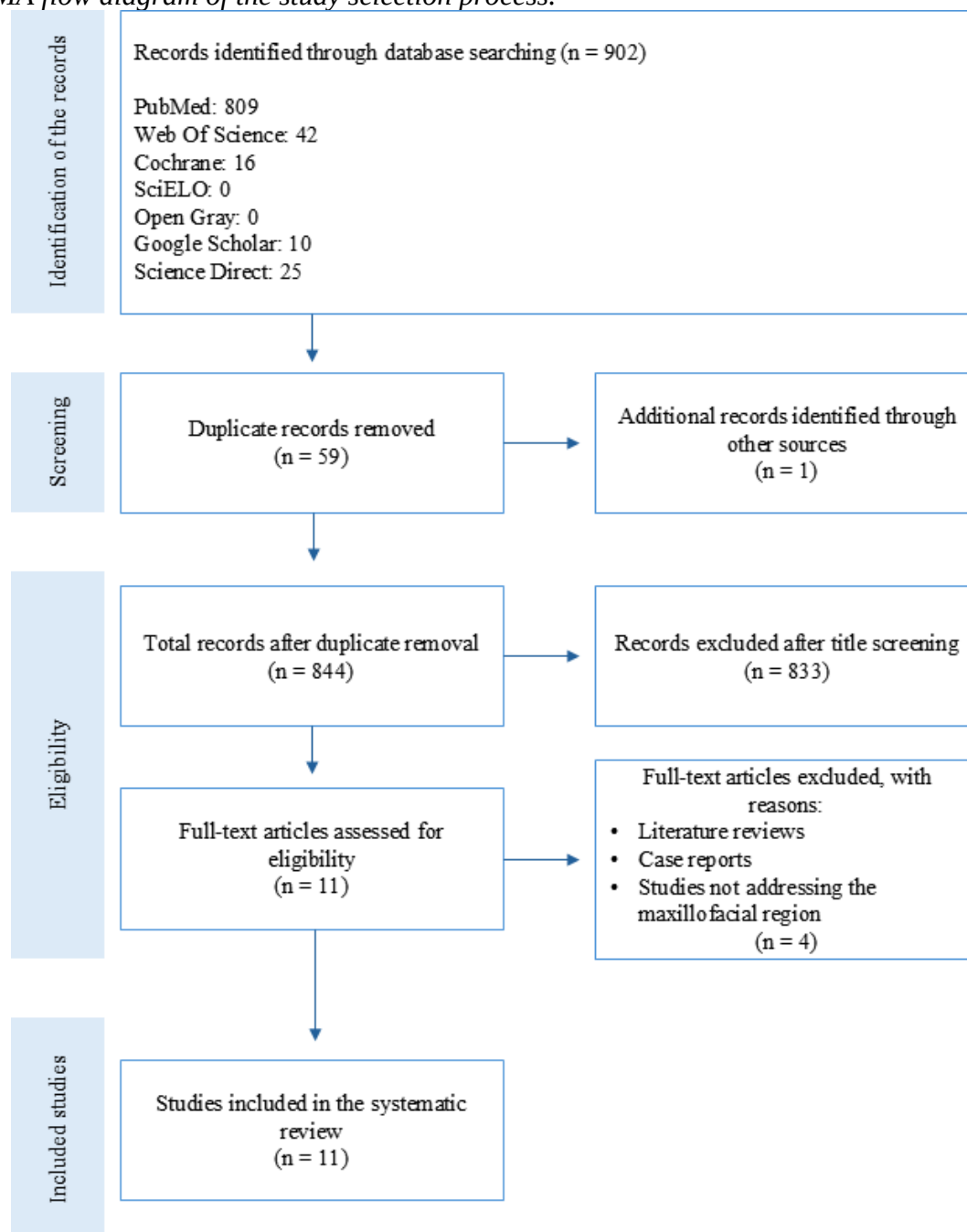
RESULTS

A total of 902 articles were identified. After applying the inclusion and exclusion criteria, seven studies were selected for the final sample of this systematic review. The study selection process was documented using the PRISMA flow diagram. In addition, to increase the comprehensiveness of the search, the reference lists of the included articles were manually screened. As a result, one additional study was identified through manual reference searching, assessed for eligibility, and included because it met the predefined inclusion criteria. The

identification and inclusion of this additional study are presented in Figure 1, under the section "Additional records identified through other sources."

Figure 1

PRISMA flow diagram of the study selection process.



The selected studies were organized in Table 2 according to journal, title, authors/year, sample, type of botulinum toxin, objectives, and main findings. The included studies were

randomized clinical trials conducted between 2004 and 2020.

Table 2

Studies included in the systematic review.

Journal	Title	Authors/Year	Sample	Type	Objectives	Main Findings
American Academy of Neurology	A double-blind placebo-control led botulinum toxin B for sialorrhea in Parkinson's disease	Ondo <i>et al.</i> , 2004	16 patients	Botulinum toxin type B	To determine whether BTX-B is a safe and effective treatment for sialorrhea in patients with Parkinson's disease (PD).	Anatomically guided BTX-B injections into the parotid and submandibular glands effectively improved sialorrhea without worsening dysphagia in patients with Parkinson's disease (PD).
Child Neurol	Botulinum Toxin Type A on Oral Health in Treating Sialorrhea in Children With Cerebral Palsy: A Randomized, Double-Blind, Placebo-Controlled Study	Wu <i>et al.</i> , 2011 ⁽¹⁷⁾	20 patients	Botulinum toxin type A	To determine the therapeutic effect of low-dose, ultrasound-guided BTX-A injections into the bilateral parotid and submandibular glands.	A significant reduction in salivary flow rate was observed at the 1- and 3-month follow-up visits in the BTX-A-treated group. The protocol effectively controlled sialorrhea while maintaining oral health.
PLOS One	Safety Efficacy Botulinum Toxin and of to Preserve Gland Function after Radiotherapy in Patients with Head and Neck Cancer: A Prospective, Randomized, Placebo-Controlled, Double-	Teymoortash <i>et al.</i> , 2016	12 patients	Botulinum toxin type A and botulinum toxin type B	To investigate the safety and efficacy of BTX-A and BTX-B in preserving salivary gland function after radiotherapy in patients with head and neck cancer.	This study demonstrated that BTX can be safely combined with radiotherapy and chemotherapy. However, the optimal BTX dose and timing of injection require further investigation to better evaluate its efficacy.

	Blinded Phase I Clinical Trial					
	Botulinum Toxin and of to Preserve Gland Function after Radiotherapy in Patients with Head and Neck Cancer: A Prospective, Randomized, Placebo-Controlled, Double-Blinded Phase I Clinical Trial	al., 2016 ⁽¹⁸⁾		toxin type A and botulinum toxin type B	the safety and efficacy of BTX-A and BTX-B in preserving salivary gland function after radiotherapy in patients with head and neck cancer.	demonstrated that BTX can be safely combined with radiotherapy and chemotherapy. However, the optimal BTX dose and timing of injection require further investigation to better evaluate its efficacy.
DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY	Cost-effectiveness of botulinum neurotoxin A versus surgery for drooling: a randomized clinical trial	Bekker <i>et al.</i> , 2020 ⁽¹²⁾	82 patients	Botulinum toxin type A	To compare the cost-effectiveness of BTX-A injections with bilateral submandibular duct ligation for the treatment of severe drooling.	The additional cost of bilateral submandibular duct ligation was partially offset by its higher long-term treatment success rate compared with BTX-A.

Elsevier – Parkinsonism & Related Disorders	Long-term incobotulinum toxin treatment chronic sialorrhea: Efficacy A for and safety over 64 weeks	Jost <i>et al.</i> , 2020 ⁽¹⁹⁾	148 patients	Botulinum toxin type A	To investigate the efficacy and safety of repeated BTX-A injections for chronic sialorrhea over a 64-week period.	The data support the long-term efficacy and safety of repeated BTX-A treatment for sialorrhea.
SIAXI	Placebo-controlled, randomized, double-blind study of incobotulinum toxin A for sialorrhea	Jost <i>et al.</i> , 2023 ⁽²⁰⁾	184 patients	Botulinum toxin type A	To investigate the efficacy and safety of BTX-A for the treatment of chronic sialorrhea due to Parkinson's disease (PD), atypical parkinsonism, stroke, or traumatic brain injury.	BTX-A 100 U was an effective and well-tolerated treatment for chronic sialorrhea in adults.
Head & Neck	Botox for the prevention of radiation-induced sialadenitis and xerostomia in head and neck cancer patients: pilot study	Nieri <i>et al.</i> , 2023	20 patients	Botulinum toxin type A	To determine the safety of BTX-A and its potential effect in mitigating radiotherapy (RT)-induced sialadenitis in patients with head and neck cancer.	BTX-A can be safely administered into the salivary glands before external beam radiotherapy, with no observed complications or adverse effects.

The Cochrane Handbook for Systematic Reviews of Interventions was used to assess the risk of bias in the selected studies, and the results are presented in Table 3.

Table 3

Cochrane Risk of Bias (RoB 1.0).

Article	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Ondo <i>et al.</i> , 2004	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear
Wu <i>et al.</i> , 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Teymoortash <i>et al.</i> , 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bekkers <i>et al.</i> , 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jost <i>et al.</i> , 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jost <i>et al.</i> , 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nieri <i>et al.</i> , 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

The studies included in this systematic review were published in international journals and were all available in English. The randomized clinical trials evaluated the application of botulinum toxin in different clinical settings related to sialorrhea and associated conditions.

The sample size among the selected studies ranged from 12 to 184 participants. Among the studies, the smallest sample was reported by Teymoortash *et al.* (2016), who evaluated 12 patients regarding the preservation of salivary gland function following radiotherapy. In contrast, the largest study was conducted by Jost *et al.* (2023), including 184 patients with chronic sialorrhea associated with various neurological disorders. These findings demonstrate the wide range of clinical applications and patient populations investigated, reinforcing the relevance of botulinum toxin as a safe and effective therapeutic intervention across diverse clinical settings.

Most studies presented a low risk of bias across nearly all assessed domains, supporting the reliability of the reported findings. However, the study of Ondo *et al.*, (2004) showed an unclear risk of bias in some domains, including random sequence generation, allocation

concealment, and other sources of bias, indicating potential methodological limitations that may influence the interpretation of its findings. The consistency of the results among the remaining studies strengthens the overall body of evidence while highlighting the importance of considering potential methodological limitations in the overall interpretation of the data.

DISCUSSION

The literature reviewed indicated that the therapeutic use of botulinum toxin is of great importance for maintaining oral health in individuals affected by sialorrhea, as this salivary gland disorder leads to several oral manifestations that negatively impact the oral health of critically ill patients. To discuss this topic, two thematic categories emerged: (1) Use of Botulinum Toxin for the Treatment of Sialorrhea and (2) Botulinum Toxin Injection and Administration Protocols.

1. Use of Botulinum Toxin for the Treatment of Sialorrhea

Sialorrhea is a condition commonly observed in patients with Parkinson's disease (PD), atypical parkinsonism, stroke, or traumatic brain injury (TBI), and treatment with botulinum toxin type A (BTX-A) has been shown to be effective and well tolerated (Jost *et al.*, 2020).

Conservative treatments for sialorrhea include oral anticholinergic and antihistamine medications; however, there is limited formal evidence supporting their efficacy, and they are often poorly tolerated. Invasive procedures, such as parotidectomy, salivary duct ligation, and radiation ablation, have occasionally been employed. More recently, botulinum toxin (BTX) has emerged as an effective alternative for controlling salivary secretion (Bekkers *et al.*, 2020).

The use of botulinum toxin type B (BTX-B) has also been shown to be effective in the treatment of sialorrhea in patients with Parkinson's disease, resulting in significant improvements in clinical salivation scores and patient-reported satisfaction. The time to peak response was short, and clinical effects lasted between 12 and 20 weeks. Although mild adverse events were reported, treatment was well tolerated and demonstrated significantly greater efficacy than placebo across all evaluated outcome measures (Ondo *et al.*, 2011).

The study conducted by Nieri *et al.* (2023) aimed to evaluate the efficacy of BTX-A in preventing radiation-induced sialadenitis and xerostomia in patients with head and neck cancer. The results demonstrated that although salivary flow significantly decreased in both the BTX and control groups immediately after radiotherapy (RT), the BTX-treated group exhibited

stabilization of salivary flow following the initial decline, whereas the control group continued to experience a progressive reduction. Furthermore, the inflammatory marker CXCL-1 was significantly reduced in the BTX group, suggesting an anti-inflammatory effect associated with the intervention.

The administration of botulinum toxin type A in children with cerebral palsy was effective in significantly reducing salivary flow one and three months after treatment compared with the control group, demonstrating its usefulness in the management of sialorrhea. However, subjective sialorrhea scores and salivary characteristics, including biochemical composition and levels of cariogenic bacterial colonies, did not differ significantly between groups throughout the follow-up period, suggesting that the therapeutic effect was limited to reducing salivary flow without altering other salivary parameters (Wu *et al.*, 2011).¹

Bekkers *et al.* (2020) compared the cost-effectiveness of BTX-A injections with bilateral submandibular duct ligation for the treatment of severe drooling. Their findings indicated that although duct ligation incurred higher initial costs, these were partially offset by its higher long-term treatment success rate compared with BTX-A.

A study conducted by Teymoortash *et al.* (2016) investigated the safety and efficacy of botulinum toxin for preserving salivary gland function following radiotherapy in patients with head and neck cancer. The authors demonstrated that BTX-A can be safely combined with radiotherapy, thereby reducing radiation-induced toxicity in salivary gland tissue.

2. Botulinum Toxin Injection and Administration Protocols

Ultrasound-Guided Botulinum Toxin Injection

Several authors emphasized the importance of ultrasound guidance during botulinum toxin injection into the salivary glands, improving both precision and safety. Jost *et al.* (2020) introduced a flexible protocol in which ultrasound guidance was used in 56.5% of cases to identify the parotid and submandibular glands. This technique was complemented by standard anatomical landmarks, including the angle of the mandible for the parotid glands and the area medial to the body of the mandible for the submandibular glands, allowing adaptation according to clinical circumstances and available resources.

Nieri *et al.* (2023)¹ also used ultrasound guidance to administer 50 U of BTX-A into each submandibular gland of patients with head and neck cancer. This protocol ensured anatomical

accuracy and procedural safety, resulting in stabilization of salivary flow and reduction of glandular inflammation.

Similarly, Teymoortash *et al.* (2016) performed ultrasound-guided injections of BTX-A and BTX-B into the submandibular glands 14–21 days before radiotherapy and chemotherapy, thereby improving tolerance to oncologic treatment.

Wu *et al.* (2011) adapted BTX-A administration for children with cerebral palsy by using ultrasound guidance to ensure injection accuracy and minimize procedural risks, while adjusting doses according to body weight.

2. Anatomical Landmark-Based Protocols and Specific Applications

Ondo *et al.* (2004) investigated BTX-B administration using anatomical landmarks to guide injections, delivering 1,000 U into each parotid gland and 250 U into each submandibular gland. Injection accuracy was ensured through the use of tuberculin syringes, and the results demonstrated effective control of sialorrhea with high-dose BTX-B.

In another study, an outpatient protocol was adopted for BTX-A administration into the submandibular glands using 25 U per gland diluted in saline solution. This specialized technique demonstrated a favorable safety profile and consistent outcomes in the management of sialorrhea (Bekkers *et al.*, 2020).⁽¹²⁾

3. Flexible Protocols and Recent Studies

In the most recent study by Jost *et al.* (2023), BTX-A was injected into the parotid and submandibular glands at doses of either 75 U or 100 U, administered through four injection sites per gland. This protocol ensured effective blinding and optimized toxin distribution, resulting in a significant reduction in salivary production. The flexibility of the protocol enabled effective management of sialorrhea across a broad range of clinical conditions, illustrating the evolution of injection techniques.

Collectively, these protocols reflect the evolution of botulinum toxin therapy for the management of sialorrhea, ranging from ultrasound-guided techniques to anatomical landmark-based approaches, all emphasizing safety, precision, and adaptation to individual patient needs.

CONCLUSION

The present study highlights the importance of precise techniques tailored to the specific needs of each patient, demonstrating that botulinum toxin is an effective treatment for the management of sialorrhea.

The use of ultrasonography as an adjunctive tool was consistently reported, reinforcing its relevance in clinical practice for ensuring safe and effective outcomes. In this context, it is essential that dentists specialized in Hospital Dentistry possess both theoretical knowledge and practical expertise on this subject to ensure appropriate patient management and contribute to the maintenance of oral health in critically ill patients.

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