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REVIEW

Direct Applications of Non-Thermal Atmospheric Pressure Plasma: An Emerging Therapeutic Era in Ophthalmology

Aisha S Al-Battashy[1], Arwa A Al-Mujaini[2], Abdullah S Al-Mujaini[3]

[1]PGY2, Ophthalmology Residency Program, Oman Medical Specialty Board, Muscat, Sultanate of Oman; [2]PGY2, Radiology Residency Program, Oman Medical Specialty Board, Muscat, Sultanate of Oman; [3]Professor, Department of Ophthalmology, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Sultanate of Oman

Correspondence: Abdullah S Al-Mujaini, Department of Ophthalmology, College of Medicine and Health Sciences, Sultan Qaboos University, PO Box: 35, Al Khoud, Muscat, PC 123, Sultanate of Oman, Tel +968 99317397, Fax +968 24144864, Email abdullah.almujaini@gmail.com

Abstract: This article explores the burgeoning role of cold atmospheric plasma (CAP) in ophthalmology. The versatile nature of CAP has transformed various facets of eye care, offering novel possibilities across different clinical domains. From sterilizing surgical instruments without compromising their integrity to effectively managing challenging corneal diseases like microbial keratitis and fungal infections, CAP has shown promising results. Moreover, its potential role in promoting corneal wound healing, facilitating corneal transplants, and enhancing outcomes in cataract surgeries deserves attention. The low-tension plasma blade (ie, the Fugo blade™, Medisurg Ltd. Norristown, PA), a controlled and precise form of CAP, has emerged as a game-changer in delicate eye surgeries. Its unmatched precision, minimal tissue damage, and surgeon-friendly nature have revolutionized ophthalmic procedures, including ptosis correction, dry eye treatment, and conjunctival cyst ablation. Despite conflicting findings on the efficacy of this technology in certain aspects, the extensive body of research on CAP underscores its potential for wider ophthalmic integration. Further investigation, including human trials, is crucial for understanding the in vivo safety profile of CAP for ophthalmic applications and optimizing its use, potentially revolutionizing ocular disease management and improving patient outcomes.

Keywords: cold atmospheric plasma, low-tension plasma blade, fugo blade, sterilization and disinfection techniques, wound healing, ablation and dissection

Introduction

The field of ophthalmology has witnessed remarkable advancements in recent years, driven by innovative technologies and novel approaches aimed at enhancing the diagnosis and treatment of ocular diseases. One such innovation that has garnered increasing attention is the application of cold atmospheric plasma (CAP). Plasma is the fourth neutral state of matter and contains ionized particles that can interact with living cells. These include charged species (ions and electrons), excited neutral species originating mainly from the working gas involved in the plasma process, reactive oxygen (ROS) and nitrogen species (RNS), and electromagnetic radiation in the visible, ultraviolet, and infrared fields.[1] Depending on the gas composition, the relationship and amount of the plasma compounds mentioned above may vary significantly.[2]

The main biological effects of plasma most relevant to medical applications stem from its ability to inactivate a wide range of microorganisms, including multidrug-resistant ones, to stimulate cell proliferation, thereby promoting tissue regeneration, and to inactivate or kill cancer cells by inducing programmed cell death (apoptosis).[3] Data collected from various research projects on cultivated microorganisms and human cells has identified two distinct but interconnected basic principles of this biological action: 1) inducing changes to the liquid environment of cells; and 2) increasing either cellular repair processes or inducing apoptosis as a direct consequence of the formation of ROS and RNS.[3]

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The versatility of cold plasma presents numerous possibilities across various fields. While it has found applications in various clinical contexts, its use in ophthalmology is established in some scenarios, while still somewhat experimental in others. One historically significant moment, widely recognized as the starting point of ophthalmologists' experimentation with cold plasma, is Dr. Richard Fugo's invention of the low-tension plasma (LTP) blade.[4] However, compared to its extensive utilization in other fields, there remains limited published research on ophthalmologic applications. Such exploration is relatively recent, and research is ongoing to understand the potential and safety of this technology. Only in the past decade have there been a significant number of publications, which we will discuss below.

Clinical Applications

Before understanding its applications, it is important to familiarize oneself with available forms of cold plasma and their unique properties. This will in turn help us understand their applications better.

CAP in its raw state involves plasma energy that is dispersed, thereby allowing for the ablation of microbes and sterilization of organic or inorganic matter while simultaneously preserving the integrity of the material being treated.[3] Another form of cold plasma is the LTP blade, commonly known as the Fugo blade™ (Medisurg Ltd., Norristown, PA), which functions as an excimer laser for cutting tissues. Plasma produced from this source consists of a controlled, localized energy beam that has the ability to precisely cut through tissue without causing surrounding inflammation or tissue damage. Plasma energy from the blade ablates the bonds of biological macromolecules, breaking them into small molecular fragments.[5] The Fugo blade is composed of a power supply, a plasma generator, and a handpiece with an electrode tip. The power unit converts electricity into high-frequency pulses, which the plasma generator uses to create cold plasma from gases like argon or helium at low pressures. This plasma is directed through the handpiece to interact with tissues during surgery.[4]

Comparing low-tension plasma (LTP) and cold atmospheric plasma (CAP) reveals their distinct operating principles and applications. LTP, exemplified by the Fugo blade, generates plasma with low voltage, enabling precise tissue interactions in surgery through controlled plasma discharge using dielectric barrier discharge (DBD) technology.[4] Cold atmospheric plasma (CAP) technologies, such as DBD plasma or atmospheric pressure plasma jets (APPJ), create plasma at room temperature without requiring a vacuum or specific gases, making them versatile for medical applications like wound healing and tissue sterilization. CAP's principle involves producing reactive species that interact with tissues without causing thermal damage.[3]

Dispersed Cold Atmospheric Plasma

We will begin with a discussion on the applications of dispersed CAP in ophthalmologic practice. Firstly, as in other surgical fields, dispersed CAP has been proven to effectively sterilize surgical tools for use in surgical ophthalmology.[6] Indeed, CAP can eliminate all resistant pathogens, including viruses, prions, and endotoxins, without damaging the instrument in question. This presents a significant advantage over conventional sterilization methods like the autoclave. Moreover, thanks to its ability to operate without heat or moisture, CAP can sterilize even plastic instruments and surgical facilities without compromising their integrity.[6]

The use of CAP has also led to significant advancements in the management of corneal diseases. One notable example is in the treatment of microbial keratitis, a particularly challenging corneal ailment associated with a high risk of complications.[7] In such cases, CAP has demonstrated effectiveness in eradicating the pathogens responsible, all while preserving the structural integrity of the cornea.[8] It can work in conjunction with traditional antimicrobial treatments, enhancing the effectiveness of antibiotics and acting as a formidable adversary against even the most resilient microbes.[9–11] In one study, Carr et al reported that the use of CAP, either alone or in combination with antibiotics, led to a substantial reduction in bacterial levels and an improvement in clinical outcomes in rabbits with keratitis caused by both methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[9] In a separate animal model study, Nikmaram et al concluded that both in vitro and in vivo applications of CAP effectively neutralized the fungal pathogen in the treatment of keratitis secondary to *Aspergillus fumigatus*.[10] Reitberger et al conducted the first in-human case series and experimental study of argon cold plasma in four patients with therapy-resistant corneal ulcers caused by common pathogens; the results showed that all patients significantly improved following CAP treatment combined with antibiotic therapy.[11]

In a study by Brun et al (2012), researchers investigated the effects of CAP on ocular cells, observing changes in cell viability, morphology, and functionality with varying CAP exposure times. They found that short CAP exposures effectively disinfect ocular cells and tissues without significant damage.[12] Furthermore, several other studies support the notion of CAP's efficacy and safety in ophthalmology. Nejat et al (2021) conducted an animal study evaluating the safety of atmospheric low-temperature plasma (ALTP) on the conjunctiva, with a 6-month follow-up period, and found no significant histopathological findings, indicating a favorable safety profile.[13] Rosani et al (2015) investigated the transcriptional changes induced by atmospheric-pressure cold plasma in ex vivo human corneas, providing additional insights into the molecular mechanisms underlying CAP's effects on ocular tissues. These studies collectively underscore the potential of CAP as a safe and effective modality for disinfection and sterilization of the ocular surface.[14]

Additionally, CAP holds promise in facilitating corneal wound healing by promoting cell migration and proliferation, thus aiding in the repair of corneal injuries and expediting the recovery process.[15] Despite limited research, CAP holds potential for use in corneal transplants, such as penetrating keratoplasty, a high-risk ophthalmic procedure with a lengthy recovery period. Principally, CAP can be used to sterilize donor graft tissue, thereby reducing post-surgery infection risks.[6] Moreover, when applied to the graft-host interface or surgical site, it can enhance cell migration, promote tissue regeneration, and contribute to overall healing, potentially leading to a quicker recovery and better corneal integration.[16] Additionally, the antimicrobial and anti-inflammatory qualities of this modality can help manage post-surgery complications, such as infection, graft rejection, or corneal edema, by disinfecting the ocular surface, regulating inflammation, and creating a favorable healing environment.[12,17] Beyond this, possible corneal applications of CAP extend to sterilizing contact lenses and even preserving transplant materials such as corneal grafts and amniotic membranes.[6,18]

Cataract surgery is a routine ophthalmic procedure performed regularly in well-established tertiary care hospitals; however, an unavoidable long-term complication following cataract surgery and intraocular lens implantation is the development of posterior capsular opacification (PCO).[19] The type of intraocular lens material and its edge design have been shown to influence the timing of PCO development.[20] Specifically, CAP has been studied for its antifibrotic properties, which may help inhibit or reduce capsular fibrosis, potentially enhancing post-surgery visual outcomes.[21] A study investigating the effects of CAP on human anterior lens epithelial cells (LECs) cultured ex vivo demonstrated that targeted micropipette plasma treatment can selectively induce the demise of LECs, potentially preventing their migration to the posterior lens capsule and reducing PCO formation if utilized in vivo.[22]

Importantly, CAP may also have an invaluable application in the realm of ocular oncology as a noninvasive supplementary method to ensure tumor margin sterilization during eyelid tumor surgery. Moreover, several studies have proven the ability of CAP to selectively target cancer cells in vitro, allowing for specific cancer cell or tumor tissue demise without affecting the surrounding healthy cells and tissues.[23] In one study, cold plasma application successfully selectively impaired head and neck squamous cell carcinoma (SCC) cell lines, while having a minimal effect on normal oral cavity epithelial cell lines.[24] In another study, CAP was shown to successfully prompt the senescence of melanoma cells.[25] Additional in vitro studies corroborate the potential impact of CAP as a promising therapeutic approach in the treatment of SCC and melanoma.[26,27] Cheng et al also reported the direct and indirect effects of CAP on glioblastoma cancer cells in vitro; their initial observations establish CAP as a potentially useful ablative therapy tool in the treatment of brain cancer.[28] Moreover, as previously mentioned, CAP has been shown to expedite wound healing, a useful function following surgical excision of a tumor.[17]

The Low-Tension Plasma Blade

We will now discuss the extensive application of the LTP blade in ophthalmologic practice. Introduced by Dr. Richard Fugo in the early 2000s, the LTP blade was initially designed as a surgical tool for dermatologic procedures; however, the potential of this device soon transcended its original purpose. In ophthalmology, the unparalleled precision of the blade, allowing for extremely fine and controlled incisions, made it ideal for procedures requiring meticulous precision such as delicate eye surgeries. This innovation revolutionized ophthalmic surgery, offering a safer and more refined approach, and earning recognition as a groundbreaking advancement in the field.[4]

The superiority of the LTP blade over other forms of laser technologies stems from several distinctive advantages. Among these, the capability to selectively ablate tissue without causing thermal damage to surrounding areas stands out,

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alongside its capacity for controlled hemostasis, aiding clear visualization during surgery. Moreover, its exceptional precision in tissue cutting and dissection makes it particularly well-suited for delicate ophthalmic surgical procedures, and potentially contributes to more favorable postoperative outcomes.[29] During evisceration, the LTP blade offers vital benefits as a result of its capacity for precise dissection, especially during the initial incision to access the eye's interior structures, minimizing tissue trauma and ensuring a clean and controlled procedure.[4] Additionally, it assists in removing specific tissues and shaping the scleral shell before implant placement, enabling surgeons to perform meticulous, accurate maneuvers.[4] Although dependent on the individual surgeon's preference and case specifics, the tool is recognized for being easy to master and handle; moreover, its use has been linked to reduced postoperative inflammation and edema, and quicker tissue re-epithelialization and wound healing.[4]

Specifically, the Fugo blade™ (Medisurg Ltd.) has been approved by the US Food and Drug Administration (FDA) for use in cataract and glaucoma surgery.[30,31] However, its versatility extends to numerous other ophthalmic applications. To begin with, the blade has demonstrated potential in various procedures in the field of oculoplasty. One extraocular application is in ptosis correction surgery via conjunctival route levator plication, a suture-less and minimally invasive procedure that takes only a few minutes.[32] It has also proven effective as a noninvasive method of performing an orbicularis oculi myectomy to treat benign essential blepharospasm.[33] Another common application is in the treatment of ocular surface diseases, such as dry eye, trichiasis, and entropion. In one clinical case series, Nejat et al reported the effectiveness of plasma-assisted noninvasive surgery (PANIS) as a temporary approach for treating dry eye disease, with patients showing significant symptomatic and clinical improvement.[34] In cases of trichiasis, the LTP blade can be used to ablate the hair follicle without causing inflammation in the surrounding structures or tissue; similarly, entropion surgery has also been enhanced by using the LTP blade.[4,35]

In conditions like Bell's palsy, tarsorrhaphy is a valuable procedure to prevent exposure keratopathy. In such cases, the LTP blade can be used to ablate the lid margins to cause adhesions, thereby offering an alternative to the conventional lid suturing method.[4] In patients with recurrent acquired nasolacrimal obstruction following failure of conventional dacryocystorhinostomy, LTP ablation (ie, coablation) has been proven to have better long-term efficacy in the alleviation of symptoms compared to conventional methods.[36] Nejat et al used the LTP blade to develop a novel, minimally invasive approach to conjunctival cyst ablation, with no complications or cases of cyst recurrence reported.[37] Recently, the LTP blade has also been explored as an alternative surgical approach for managing conjunctivochalasis. In one study, Ucar concluded that plasma-based conjunctivoplasty represents a simple, minimally invasive surgery, resulting in reduced intra- and postoperative discomfort and quicker patient recovery compared to conventional surgical methods.[38] Findings from Jadidi et al support this idea, presenting a case series in which PANIS displayed substantial potential as a noninvasive and dependable approach to addressing conjunctivochalasis.[39]

Pterygium surgery also has the potential for enhanced outcomes with the introduction of CAP. A recent publication assessed the safety and effectiveness of a low-temperature plasma surgical system for excision of the pterygium.[40] The results indicated that the system was safe, demonstrated effective intraoperative hemostasis, and had better postoperative results with lower inflammation compared to conventional surgical methods, suggesting that the system holds potential as a safe and effective alternative for pterygium treatment.[40] The LTP can also be utilized for the purposes of ocular surface benign lesion ablation. Benign nevi located over the conjunctiva or lid margin can be ablated with the LTP blade without any damage to the surrounding tissue, resulting in the near-complete disappearance of the lesions and a cost-effective and minimally invasive procedure.[41]

The potential applications of the LTP blade in the field of ocular oncology are particularly groundbreaking. Cumulative reports have demonstrated the utility of the LTP blade in the treatment of eyelid, conjunctival, and intra-orbital malignancies, employed either as a standalone approach for tumor ablation in very localized, unresectable tumors, or as a supplementary method to ensure tumor margin sterilization post-resection.[4] Furthermore, CAP offers the potential for minimally invasive treatment of intra-orbital and nasolacrimal sac tumors. For instance, in an in vivo exploration, Robert et al found that non-thermal CAP devices allow for plasma to be delivered to treat pancreatic and colorectal cancers via an endoscopic approach, reducing the necessity for extensive surgical intervention.[42]

Moreover, the LTP blade has shown valuable applications in cataract surgery, the most common ophthalmic procedure, receiving FDA approval for this indication in the early 2000s.[31] During capsulorrhexis, the LTP blade employs an incising filament as thin as a human hair in without the need for a red reflex or viscoelastic, resulting in resistance-free ablation of the anterior capsule.[43] This capability extends to particularly challenging cases, including patients with weak zonules, dense anterior capsules, small pupils, or thick pupillary membranes.[35] The LTP blade is also effective for anterior capsulorrhexis in children, overcoming the usual difficulty posed by the enhanced elasticity of the pediatric lens capsule.[44] Researchers have even employed the LTP blade in pediatric cataract cases with florid anterior persistent hyperplastic primary vitreous.[45,46] In one study, the authors reported no cases of intraoperative intraocular hemorrhage, and vision improving to more than 20/60 in 50% of pseudophakic patients, following utilization of the LTP blade during anterior and posterior capsulotomy.[45] Moreover, use of the LTP blade in patients requiring cataract surgery post-keratoplasty does not lead to corneal decompensation within 10 years of surgery.[35]

Glaucoma surgery may also stand to benefit from the utilization of the LTP blade, contributing to the development of multiple innovative techniques.[47] To start, transciliary filtration (also known as Singh filtration) has emerged as a highly effective alternative to trabeculectomy. This procedure involves creating a conjunctival bleb using the LTP blade to ablate a small scleral reservoir, a minimally invasive and time-efficient process.[35] The enhanced control of intraocular pressure and deceased likelihood of overfiltration contribute to more predictable postoperative results.[35] The LTP blade has also been reported to play a role in the surgical management of hemophthalmos.[4] Another application in glaucoma surgery is in goniotomy utilizing an *ab interno* approach, involving removal of parts of the trabecular meshwork to create a direct path from the front chamber of the eye to Schlemm's canal.[48] In this procedure, the LTP blade offers multiple benefits, such as allowing for internal filtration without the creation of an external bleb, which may help to reduce the risk of hypotony. Additionally, it has the potential to streamline the surgical procedure and provide protection to the conjunctiva.[4]

During intraocular procedures, the LTP blade can also be used to ablate iris tissue when performing an iridectomy or iridotomy.[4] It is also documented to have a role in pupilloplasty.[35] Last but not least, this innovative device been used in pediatric and adult strabismus surgery. Compared to conventional methods, Singh et al enumerated numerous advantages of the LTP blade for this indication, emphasizing improved surgical control, enhanced visualization of structures due to better intraoperative hemostasis, and reduced operative time.[48]

A Caveat

Numerous publications have highlighted the potential applications of this emerging energy source in ophthalmic practice, although certain studies have raised doubts regarding specific aspects. In the context of strabismus surgery, several drawbacks associated with the LTP blade have been reported, including uncertain control over the depth of tissue removal, the possibility of scar tissue formation over the opening, and limitations in lowering eye pressure due to episcleral venous pressure.[48] Furthermore, Alhabshan et al reported that utilization of CAP did not contribute significantly to corneal wound healing in rabbits.[49]

The long-term effects of CAP on human tissue remain an area of active research. Concerns arise regarding its antimicrobial properties' impact on natural tissue microbiota, the potential for excessive inflammatory responses, risks of tissue damage with prolonged or inappropriate application, and the need to assess any genotoxic or carcinogenic effects over time. The article by Rutkowski et al (2020) is the only study done to date that evaluates the long-term effect of in vivo application of CAP. It included a follow-up and assessment of five probands who received CAP five years prior to evaluation. Through comprehensive analyses, the authors conclude that CAP exhibits low genotoxic and cytotoxic effects, making it a promising and safe technology for various medical applications, including wound healing, infection control, and tissue regeneration. However, they emphasize the need for continued research and vigilance in monitoring potential risks associated with prolonged CAP exposure in clinical settings. Further comprehensive studies, including longitudinal assessments and controlled trials, are necessary to fully understand CAP's safety profile, efficacy, and potential risks when applied to human tissue over extended periods.[50]

Nonetheless, despite these conflicting findings, the extensive body of research on the properties and current applications of this technology suggests promising potential for CAP in unexplored areas within a diverse range of ophthalmic procedures. For example, in corneal transplants, utilization of the LTP blade during the trephination process or the application of dispersed CAP to manage post-transplant complications like corneal infections and rejection holds promise, although further investigation remains essential.[6,12,16–18,29]

Conclusion

The advancement of medical practices hinges on our ability to embrace evolving technologies. Overall, CAP has demonstrated considerable clinical potential across various ophthalmic subspecialties. However, refining our clinical approach based on emerging insights is imperative. The current state of research regarding ophthalmic applications of CAP necessitates more comprehensive human trials to ascertain its safety profile in vivo and comprehend its specific tissue interactions for treating diverse pathologies. As new research comes to light, we anticipate the evolution of CAP technologies, widening its scope in managing ocular diseases, and deepening our understanding of its long-term safety and efficacy. Integrating CAP into routine ophthalmic practice could potentially revolutionize the field by enhancing treatment outcomes, mitigating complications, and ultimately improving the overall patient experience.

Abbreviations

CAP, Cold atmospheric plasma; FDA, Food and Drug Administration; LECs, Lens epithelial cells; LTP, Low-tension plasma; PANIS, Plasma-assisted noninvasive surgery; PCO, Posterior capsular opacification; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; SCC, Squamous cell carcinoma.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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