Milestones of Medical Ozone

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Medical Ozone as a Focal Point of Criticism

If we could either press medical ozone into tablets, pack them at the right dosages, or store it in the form of stable infusion solutions, or even sell it as an OTC product — many of our problems would be solved. Since its discovery by SCHÖNBEIN in 1839, ozone, and particularly medical ozone, has always had a negative image. This was why, already in 1935, JUSTUS VON LIEBIG proposed calling this Janus-like substance „ozonized oxygen" to make it less offensive. Although this sounds better, its Janus-headed nature still remains.

Since the introduction of ozone therapy into medicine during the 1950s, its value or "non-value" have been subject to heated and controversial discussions. And, naturally, particularly in the field of biological therapy methods, charlatans have found a nesting place again and again. It is against these that ozone therapy has most certainly had and still has a running battle to fight.

Nowadays, ozone therapy is understood to be a genuine treatment method in complementary medicine, encouraging the scientific dialog between traditional medicine and complementary methods. Critical discussions have activated basic research in the field of ozone therapy including the revision of highly complicated treatment methods and resulting in the exclusion of intravascular administration of O_2/O_3 gas mixtures or infusions under pressure, and the introduction of low-risk application techniques

Guidelines on hygienic procedures in extracorporeal blood treatment with ozone have been drawn up, and hygiene sets developed to guarantee the greatest possible protection against infection and a safe use of medical Ozone.

Although large-scale placebo-controlled double blind studies have not yet been conducted, we have a large number of case reports as well as controlled clinical studies, that have been a great help to standardise dosages, treatment regimens and application techniques. Ozone generators equipped with photometric measuring units here fulfil the wide range of concentration and dosage requirements for the different indications.

State of the Art

Indications and underlying active mechanisms

Over the decades, a smaller but decisive number of indications for medical ozone have crystallized, supported by a large number of case reports from hospitals and practices. The underlying physiological active mechanisms of ozone have, for the most part, been clarified up to the present, and constitute a plausible scientific background for its therapeutical application (see Table 1).

Table 1: The Indications for Ozone and its Underlying Active Mechanisms of Action

Indications	**Mechanisms**
External ulcers and skin lesions	Disinfection Wound cleansing Improved wound healing
Arterial circulatory disorders	Activation of RBC metabolism with an improvement of oxygen release Activation of ROS (reactive oxygen species) and radical scavengers
Immunodeficiency and immunodysbalance eg • Chronic forms of hepatitis B and C • Supportive therapy in cancer patients • Supportive therapy in rheumatoid arthritis	Activation of immunocompetent cells with release of cytokins such as interferons and interleukins Modulation of the immune system Increase of antioxydative capacity by activation of biological antioxidants
Inflammatory condition such as • Knee arthrosis • Gonarthrosis • Traumatic knee disorders	Antiinflammatory effect • Activation of antioxidative enzymes as radical scavengers • Activation of immunocompetent and cartilage cells with release of TGF-β
Dental medicine • Following tooth extraction • Buccal infections (eg candida) • Aphthae • Parodontosis	Disinfection Wound cleansing Improved wound healing

Application forms

Medication forms in a gaseous state are somewhat unusual, and it is for this reason that special application techniques have had to be developed for the safe use of ozone. In local applications as in the treatment of external wounds, its application in the form of a transcutaneous O_3 gas bath has established itself as being the most practical and useful method, for example at low (subatmospheric) pressure in a closed system guaranteeing no escape of ozone into the surrounding air. Ozonized water, whose use is particulary known in dental medicine, is optimally applied as a spray or compress.

Apart from rectal insufflation, principally used in the treatment of intestinal conditions, but also applied systemically, autohaemotherapy [or auto(haemo)transfusion] has established itself as the systemic therapy of choice.

A corresponding dosage of ozone gas is passed through or, more correctly, transferred (in the form of microbubbles) to 50 to 100 ml of the patient's blood in a sealed, pressureless system, thus achieving the finest possible distribution to reach the greatest possible number of red and white blood cells with the aim of activating their metabolism. In other words, the organism

acquires its own medication, the activated red blood cells and immunocompetent cells then being reintroduced via normal drip infusion. This is a markedly low-risk method when hygiene guidelines are observed, disposable units are used, and the material is ozone-resistant.
In pain therapy for the locomotory system, ozone can be applied supportively in the form of intramuscular or intraarticular injections.

Milestones in the Development of Ozone Therapy

The names *A. Wolff, Payr* and *Aubourg* will always be linked with pioneering research, especially in the field of locally applied medical ozone. For example, *A. Wolff* successfully treated putrescent wounds, suppurating bone fractures, fulminating inflammations (phlegmons) and abscesses during the First World War, publishing his results already in 1915. This field then received a major impulse through the work of the surgeon and ozone therapist *Erwin Payr*, who presented his epoch-making publication (of 290 pages) entitled „Ozone Treatment in Surgery" (*Über Ozonbehandlung in der Chirurgie*) at the 59th Meeting of the German Surgical Society (*Deutsche Gesellschaft für Chirurgie*) in 1935. This can rightly be called the real beginning of ozone therapy. Even if the actual methods have greatly changed, *Payr* already describes most of the treatment methods known today. At the same time, the French physician *Aubourg* established the „ozone enema" or rectal insufflation method, making use of its local effect in infectious diseases of the intestine, as well as – already - its systemic effect.

However, it was even further into the 20th Century, ie not until the 1950s, that the use of medical ozone stayed forgotten. In particular, the absence of ozone-resistant materials such as plastics, made it difficult for the practitioner to apply ozone locally in treating wounds or via rectal insufflation, as any noticeable amount of ozone in the surrounding air made work practically intolerable. When *Hänsler* presented his first medical ozone generator in 1958, which was capable of producing an ozone / oxygen mixture at therapeutically variable dosages (concentrations), and was able to make first use of ozone-resistant plastics, he could then, together with *Hans Wolff*, pave the way for ozone therapy as we know it today.

Constantly basing his research on the considerable number of publications by *Payr* and *Aubourg*, it was *H Wolff* who subsequently introduced extracorporeal blood treatment into medical practice; *Werkmeister* developed local treatment methods in the form of „subatmospheric ozone gas application", and *Rokitansky* – as a surgeon – presented the first comprehensive studies on the topical and systemic treatment of diabetic gangrene. *Knoch* then introduced rectal ozone insufflation into proctology, once more confirming its value in a controlled proctitis study.

A large number of the indications described by *Payr* had been abandoned in favour of other, more effective methods; in some indications medical ozone could be applied complementary to a basic therapy. This particularly applied in the case of rheumatism / arthritis and inflammatory diseases of the joints, for which *Fahmy* has developed a wide therapeutical concept.

Although relatively simple as regards application forms and active mechanisms, the use of ozone in dental medicine developed very modestly. As mentor, we must here mention the Swiss therapist *A. Fisch*, who himself had made *Payr* acquainted with ozone, and who presented a

doctoral thesis (1952) and first publication on the use of ozone in dental medicine in 1935. It was not until the end of the 1980s, though, that medical ozone once more became a subject of dental research (*Kirschner* and *Filippi*).

Table 2 and 3 show the development stages of indications and applications, effects and active mechanisms as milestones leading up to the present position of ozone therapy (this list makes no claim of being complete).

Pharmacological Aspects

Whereas the disinfectant properties of ozone, such as those known and clinically applied in the treatment of wounds, for example, is in the meantime able to look back on a tradition of 100 years, a detailed knowledge of the pharmacological properties of O_3 is much more recent. The first investigations on the formation of peroxides in whole blood and plasma were conducted by the work groups around *Washüttl* and coworkers, *Buckley et al., Freeman et al.* who, in conjunction with the *in vivo* investigations by *Rokitansky* and *Washüttl*, produced extensive clarity on the activation of red blood cell metabolism through ozone.

Although *Washüttl* published the first investigations on immunoactivation by the agency of O_3, it was, in this case not until *Bocci* with his study on the „Activation of Immunocompetent Cells by Ozone“ that a breakthrough was made. An initial publication in 1990 entitled „Studies on the Biological Effects of Ozone 1: Induction of Interferon-γ on Human Leukocytes“ was followed by „Studies on the Biological Effects of Ozone“ numbers 2-12, which represent a major milestone in ozone therapy up to this day:
The activation of immunocompetent cells via extracorporeal blood treatment induces, after reinfusion, a cascade of immunological reactions – thus constituting a basic pattern for explaining a major part of the indications specific to ozone therapy (see Table 1).

At the same time and in parallel to the studies conducted by *Bocci*, *Peralta* and coworkers demonstrated the activation of antioxidants and radical scavengers inherent to the organism. A preventive ozone application in the form of rectal insufflation produced an effective protection against reperfusion damage in cases of hepatic ischemia (*Peralta* et al 1999).

Ozone and prevention is also the subject of a study on lethal peritonitis first presented in 1999: a series of 5 preventive intraperitoneal ozone injections reduced lethality from 95% to 35%. At a preventively applied O_3 application (5 times **before** infection) in combination with the therapeutical application of antibiotics (2 times **after** infection), it is even possible to reduce lethality by 80% or 100%. These are the first investigations on the synergistic effect of ozone and antibiotics (*Schulz* et al 1999).
And finally, another, also preventive, effect of ozone has been found in its ability to inhibit the growth of *Plasmodium falciparum* (the pathogen of tropical malaria) in infected human red blood cells without visible haemolysis (*Lell* et al. 2001).

Table 2: Milestones of Medical Ozone. Applications and Indications

	Applications and Indications	**References**	
Surgery	Topical treatments in: severely infected wounds, phlegmons, fractures, highly infected, abscesses and fistulas.	A. Wolff E. Payr	1915 1935
	Ozone enema as rectal insufflation of the ozone oxygen mixture in proctitis, colitis and fistulas via silk catheters.	P. Aubourg	1937
Medical Ozone Generator	allows ozone application forms depending on ozone-concentration	J. Hänsler	1958
General Medicine	Major autohaemotherapy in the form of an extracorporeal blood treatment as the beginning of a low risk treatment by avoiding intravascular gas application forms.	H. Wolff	1968
Surgery	Low pressure ozone gas application as a topical treatment for: decubitus ulcers, diabetic gangrene, radiation fistulas and badly healing wounds.	H.Werkmeister	1981
	Diabetic gangrene, arterial circulatory disorders.	O. Rokitansky	1977
	Rectal application in proctitis and colitis	H.G. Knoch	1987
Orthopedics	Intraarticular injections in knee arthrosis, gonoarthrosis and rheumatoid arthritis as supportive therapy.	Z. Fahmy E. Riva-Sanseverino	1981 1989
Dental Medicine	Use of ozonized water in disinfection, parodontosis, and wound healing.	E.A. Fisch R.Türk	1935 1976
	Disinfection of rinsing systems in dental chairs Epithelial wound healing	H.Kirschner A. Filippi A.Filippi	1991 2001

Table 3: Milestones of Medical Ozone. Pharmacological Aspects

	Pharmacological effects	**References**	
Ozone and human blood	Reactions of ozone with RBC components.	Buckley et al Freeman et al.	1975 1979
	Peroxide formation in full blood and plasma.	Washüttl et al.	1977
	Influence of ozone on RBC metabolism and other blood components in vitro and in vivo.	Washüttl et al.	1986
Ozone effect on human leucocytes and other immunocompetent cells	Induction of cytokins such as interferon-γ ,- β, interleukins-1,2, 6 …. by ozone in the form of extracorporeal blood treatment as "major autohaemotherapy"	Bocci et al.	1990-2001
Blood and plasma	Activation of antioxydative enzymes and radical scavengers such as SOD, G6PDH, GSH pox or GSHred…. as protective effect in reperfusion damage by free radicals.	Leon, Bocci et al. Peralta et al.	1998 1999
Biological models and protective effects of ozone	Ozone and prevention: improvement of the survival rate in septic peritonitis by preventive ozone application in an animal model and synergistic effect with different antibiotics.	Schulz et al.	1999
	Growth inhibitory effect on plasmodium falciparum in infected red blood cells by pre-treatment with ozone.	Lell et al.	2001

Milestones in the Near Future?

Synergisms between the application of medical ozone and antibiotics open up a whole new vista, and are intended to intensify the dialogue between traditional and complementary medicine. Under the aspect of prevention, this field of indication might possibly change, ie new indications such as supportive and preventive measures will be added to classical ozone methods used up to now, and others abandoned.
A large-scale controlled clinical study, for example on chronic hepatitis B or C would here constitute the first milestone in the foreseeable future.

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