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More than one Century: Intravenous Procaine Therapy - A Systematic Review

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ABSTRACT/SUMMARY

Procaine, traditionally introduced as a local anaesthetic, has revealed over more than a century a broad spectrum of systemic, pleiotropic pharmacological properties that far exceed its classical use. More than thirty distinct biological mechanisms have now been identified, including anti-inflammatory, vasodilatory, sympatholytic, membrane-stabilising, neuromodulatory, geroprotective, and epigenetically active effects. These actions provide the scientific foundation for its expanding clinical relevance in pain medicine, neuro-regulation, cardiovascular modulation, immune-related and degenerative disorders, and complementary oncology. Within Neural Therapy, Procaine occupies a central and irreplaceable role: its segmental, interference-field–oriented and autonomic-regulatory actions uniquely position it as the primary agent capable of restoring disturbed vegetative patterns, resolving chronic dysfunctions, and re-establishing physiological self-regulation.

Beyond its local anaesthetic function, intravenous Procaine—especially in combination with bicarbonate—demonstrates profound regulatory effects on microcirculation, autonomic balance, inflammatory cascades, and mitochondrial and cellular resilience. The so-called "Procaine reset" reflects its capacity to transiently interrupt maladaptive neural patterns, modulate limbic activation, influence neurotransmitter systems, and restore homeostatic regulatory loops. The addition of bicarbonate prolongs Procaine's plasma availability, enhances its intracellular penetration, and amplifies its eutrophic and anti-inflammatory properties.

Although Procaine remains the primary therapeutic molecule in Neural Therapy, Lidocaine has also been utilised in selected clinical contexts. Lidocaine shares certain membrane-stabilising and anti-inflammatory features; however, its pharmacodynamics, autonomic influence, and regulatory depth are comparatively limited. Thus, Lidocaine may complement specific applications but cannot replace the superior vegetative-regulatory potential documented for Procaine.

Procaine-Base infusion, when properly adapted to the patient's acid–base balance, represents a cornerstone therapy in regenerative medicine, improving pain thresholds, vascular perfusion, lymphatic drainage, and emotional equilibrium. Its safety profile—documented in hundreds of thousands of applications—is exceptionally favourable, with adverse effects being rare, transient, and mild.

Given rising global burdens of chronic inflammatory, neurodegenerative, cardiovascular, metabolic, and oncologic disorders, Procaine emerges as a valuable multi-target regulatory agent capable of reducing symptom burden, complementing multimodal therapeutic strategies, and potentially lowering long-term health-care costs. Future high-quality, large-scale studies are warranted to validate its systemic mechanisms, clarify dose–response relationships, and further integrate Procaine-based therapies into modern evidence-based frameworks.

Keywords: Procaine Base infusion; Bicarbonate; Neural Therapy; Systemic regulation; lidocaine

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Introduction:

The use of infusion with the local anaesthetic lidocaine is widespread in pain therapy, anaesthesia, and neurology. Established indications include the treatment of peri- and postoperative pain [1-6], cancer-induced pain [2], neuropathy [3] and postherpetic neuralgia [4], migraine [5.6.7], and trigeminal neuralgia [8]. Ferguson and Huber also have reported a positive effect in patients with arthritis [10]. The present review addresses the local anaesthetic Procaine, whose intravenous and, particularly, infusion administration has a history of over 100 years and is characterized by specific features within its therapeutic spectrum.

The synthesis of the local anaesthetic Novocain (also known as Procaine) by Einhorn in 1905 provided us with a pleiotropic agent [10-14]. In 1906, Vishnevsky elucidated the anti-inflammatory properties of Novocain upon its application [15]. In subsequent years, several authors, including Leriche [15,16], Braun [15], and Spiess [11], documented numerous beneficial outcomes in the treatment of illnesses such as trigeminal neuralgia, migraine, throat cancer, fractures, post-operative pain, and a diverse array of dystrophic disorders. Its use has been much more developed in the field of Neural Therapy, created by the Huneke brothers, with observations of a broad spectrum of possible beneficial effects at the local, segmental, and systemic levels. A little dosage of Procaine, utilized to address neuromodulatory triggers[12] Alternatively, via intravenous injection, it might also elicit significant systemic changes.

Summarizing systemic acting features of Procaine

The Huneke brothers, in the first decades of the twentieth century, examined various effects of Procaine, discovering its potential utility in treating multiple disorders by subcutaneous, intradermal, intramuscular, and neural infiltrations. Consequently, they initially designated this therapy as "therapeutic anesthesia." Subsequently, they discovered improvements in disease when applied segmentally, as well as immediate changes at a distance (referred to as "phenomenon in seconds or lightning reaction"). They subsequently endorsed this form of therapy, now known as neural therapy [15].

Numerous Russian authors have also described Procaine's medicinal effects. Speransky, a protégé of Pavlov, published "Basis for a New Theory of Medicine" in 1936, in which he developed a new understanding of the general pathological process (acute or chronic) as a dystrophy secondary to an irritative process in the nervous system. He also verified the therapeutic properties of Procaine, which act through the nervous system to reduce or eliminate inflammation and the dystrophic process in several acute and pathologic conditions, even infectious ones [17]. Vishnevsky corroborated his discoveries by confirming Procaine's mechanism of action as exerting a eutrophic effect on the organism, which is fundamentally rooted in Pavlov's Conditioned Reflexes Theory [16,13]. The term "trophism" in this context denotes a physiological and metabolic process that maintains the normal physicochemical state of an organism's interior environment, regulated by the collective function of all innervation systems [18].

In Romania, Aslan, a protégé of neurologist Marinescu, collaborated with Pharon to examine the effects of intravenous procaine injections, using Leriche's methodology, as well as intramuscular injections. Subsequently, she concentrated her treatment on several geriatric illnesses, applying Vishnevsky's principles regarding the eutrophic effects of Procaine. She presented statistical data demonstrating the extensive therapeutic effectivity of Procaine on neurological, cardiovascular, locomotor, dermatological, and gastrointestinal disorders in the elderly [16].

Prof. Aslan, the originator of the eponymous therapy, described it as possessing a vitamin-like function in addition to its anaesthetic properties [15]. Unlike all other anesthetic agents, it induces vasodilation of arteries and capillaries [15-19]. Consequently, this therapy enables the effective targeting and enhancement of inadequately perfused tissue, particularly in instances of inflammation and discomfort. Additional advantages of Procaine include its favourable tractability and minimal toxicity, attributed to its brief half-life and plasma breakdown [14,15], as well as its capillary impermeability effect and anti-inflammatory properties [16-21], anti-oxidative and fat-reducing action [17,18,19]. Krause demonstrated that the anti-inflammatory efficacy of Procaine in rheumatic diseases was particularly pronounced when combined with alkali [29]. In addition to the impact of inhibiting voltage-dependent sodium channels, resulting in transient anesthesia [20], the supplementary effects of Procaine on cell membranes and the extracellular matrix, together with its sympatholytic properties, were also emphasized [21-26]. The impact of Procaine on mitigating the adverse effects of radiation in oncology [22,23] or strategies to enhance the efficacy of Chemotherapy are documented (See Table 1) [24,25,26,27]. Furthermore, Procaine's wide-ranging epigenetic effects have been demonstrated. It was reported in 2003 that partial

inhibition of DNA methyltransferase in vitro resulted in a growth suppression during incubation with human cancer cells [28]. A study showed that Procaine could act as a tumour suppressor gene through reducing the effect of 5-methylcytosine on general genomic DNA and cell proliferation [29]. Tada et al. discovered in human hepatoma cells a decrease in DNA methylation [30]. In vitro studies have demonstrated that Procaine suppresses the proliferation and migration of colon cancer cells and exhibits an anti-tumour activity against human stomach and lung cancer [31,32,33]. Grandhi and Perona reviewed the efficacy of Procaine in preventing cancer recurrence post-surgery in a systematic analysis in 2020 [34].

In 2016, Sabit et al. demonstrated that Procaine and carboplatin together were the most effective treatment for lowering overall DNA methylation levels in colon cancer cells. [35]. Procaine is utilized to mitigate cytotoxicity and adverse effects associated with Chemotherapy [36-41] and radiotherapy [37] in oncology. Procaine is utilized in cardiac and coronary surgery as an addition in cardioplegic solutions to inhibit neuronal ion flow and to maintain and preserve the membrane [38-42]. Gradinaru et al classified Procaine as a geroprotector due to its ability to regulate the fundamental mechanisms of aging that are prevalent in several age-related disorders (see Figure 1), including responses to oxidative damage, inflammation, hypermethylation, cellular senescence, autophagy, and tumour protection [39].

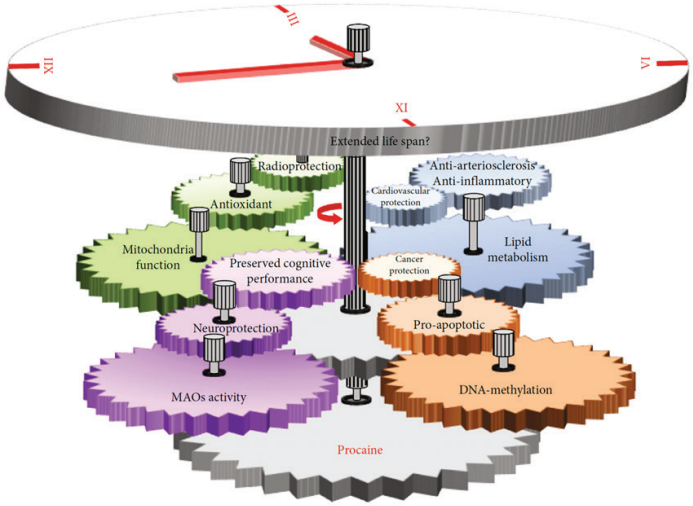


Figure 1: *New biological and pharmacological effects of Procaine—demonstrated within novel experimental approaches—which could acknowledge its consideration as a geroprotector candidate (Taken from Gradinaru et al 2021)*

Ultimately, Procaine affects the MAPK signaling pathway, among other factors. This subsequently modulates, among other factors, the expression of cytokines such as IL-6, as well as the replication of many RNA viruses, including influenza, hantavirus, respiratory syncytial virus (RSV), and SARS-CoV-2, which causes COVID-19. Procaine and the subsequently described ProcCluster® inhibit SARS-CoV-2 replication in vitro by over 90 percent (see figure 2)[40,41]. Comparable effects were observed with the Influenza A virus, the Aspergillus species, and Herpes simplex [42-44].

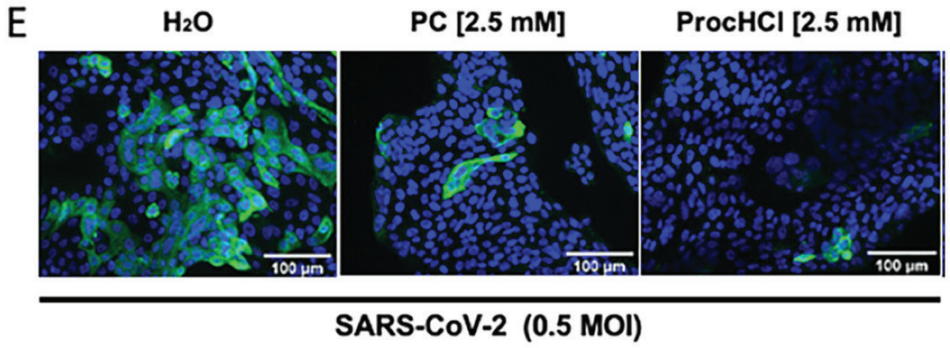


Figure 2: *For SARS-CoV-2 infection in Calu-3 cells and IAV infection in A549 cells, in the absence or presence of Procaine, immunofluorescence microscopy was performed at 24 h p.i. In untreated, SARS-CoV-2-infected samples, accumulation of spike protein is visible (H2O), which is reduced in procaine-treated samples (Taken from Häring et al. 2022)*

Table 1. *An overview according to the main systemic effects induced by Procaine:*

Pharmacological effect of Procaine	**Medical field of Use / Indication**
Local anaesthesia	Pain treatment
Vasodilatation	All kinds of vascular diseases
anti-inflammatory	Acute and autoimmune diseases
Sympatholytic	Chronic pain, stress relief
Broncho-spasmolytic	Lung diseases, asthma
Increase in coronary perfusion	Heart diseases, heart protection
Negative inotrope and antiarrhythmic	Tachycardia, heart protection
Anti-rheumatic and joint-protective	Rheumatic diseases
Anti-cancerous	Cancer prevention and treatment
Reduction of side effects from radio- and Chemotherapy	Oncology
Virustatic, inhibition of multiplication	Different kinds of viral diseases
Antifungal	Mold diseases
Anti-oxidative	Against oxidative stress
Anti-depressive, anxiety loss, emotional balancing	Dysthymia, depression, brightened mood
membrane stabilization	Transplant preservation
Influencing multiple age-related diseases	Geroprotection

Source: own elaboration

The intravenous administration and Infusion of Procaine

The injection of Procaine into a vein to produce local anaesthesia of a limb was described by Bier in 1909. A tourniquet was advised to prevent the entry of the drug into the general circulation and to prolong the anaesthesia [43]. Also, the Huneke brothers administered Procaine intravenously [1]. It has been used empirically in a wide variety of disorders, including bronchospasm, allergic conditions, myositis, diverse pain states, tinnitus, acute arrhythmias, status epilepticus, migraine, and even senility [44]. In these clinical conditions, dosages of Procaine have ranged from 20 to 50 mg given slowly intravenously, up to 4mg/kg given in 20 minutes as a so-called "Procaine unit" [45,46]. The Procaine unit, representing dosages in the range of 0.2 mg/kg in a 70 kg adult, was derived from the rat hydrolysis of Procaine hydrochloride in rabbit plasma, although it is known that hydrolysis of the drug in the human plasma is more rapid [47,48]. The only well-defined syndrome for which Procaine is currently accepted as having established therapeutic value in academic medicine is that of acute cardiac arrhythmias. Here, Procaine is given as an intravenous bolus of 300 to 500 mg, representing dosages in the range of 4 to 8 mg/kg for a 70 kg adult [49].

A brief mention of intravenous Procaine appeared in the textbook on anesthesia by *Lundy* [50], who noted the effectiveness in relieving the pruritus of jaundice. Gordon reported on intravenous Procaine analgesia for the dressing of burns in war casualties. He commented on the absence of respiratory depression often seen when large doses of Morphine are used for this purpose. It became evident that comparatively large amounts of Procaine injected intravenously could be tolerated by humans if the injection was made slowly [51]. Ameuille, a French researcher, has described one of the most promising applications of Procaine: the improvement of dyspnoea caused by several types of pulmonary and cardiac conditions. [52].

Additionally, several authors have described significant effects of intravenous Procaine in relieving sympathetic and somatic pain. Mushin and Rendell-Baker summarized the following selection: post-operative pain, pain of dressing burns, angina pectoris, thrombophlebitis, intermittent claudication of vascular disease, and arthritis [53]. Increasingly, the high anti-inflammatory potency of Procaine was recognized. Bennee reported about a complete healing from a South-African farmer aged 55 years suffering from an advanced Scleroderma. He treated the person for over three years with approximately 600 injections of Procaine 2 % intravenously, with only slight occasional reactions [54]. The action of intravenously administered

bolus doses of Procaine on 24 subjects of psychiatric patients (7 with affective disorders, 17 with borderline personality disorder) as a probe of limbic system activity was described by Kellner in 1986 [55]. Topographic EEG analysis indicated selective increases in activity over the temporal lobes. Procaine was associated with increased secretion of Cortisol, ACTH, and Prolactin.

Other uses of Procaine infusion were first described by Seifen et al. [56,57] specifically as a continuous treatment in cases of acute pancreatitis [58-60]. Also, it has been reported for use in epidural anaesthesia in infants, children, and high-risk patients, highlighting the substance's minimal toxicity [59-66]. O'Donnell et al. documented the use of procaine infusion to block cardiac nerves. [60]. For example, Layer et al. reported the results of a randomized clinical trial evaluating the effects of continuous systemic administration of 2 g of Procaine per day or placebo in 56 consecutive patients with acute pancreatitis. They were able to show that Procaine treatment was associated with a more substantial decrease in pain, and the proportion of patients hospitalized after 2 weeks was reduced to 80 % [61].

Already in 1957, Farrington reported on the importance of Procaine infusion in the management of manifestations of collagen diseases. The initial dose consisted of 500 cc. of 0.1% Procaine in normal saline or 5% glucose solution. If there were no untoward reactions to this amount, the patient was usually given 1.000 cc once per day for the succeeding 6 days at a rate of 45 drops per Minute. Of 71 cases of all types of scleroderma, about half were acrosclerotic or generalized. All patients have shown improvement in several symptoms, including difficulty with mastication, stiffness, soreness, swelling of various peripheral joints and fingers, and Raynaud's phenomenon. Similar effects they reached in three cases of dermatomyositis [62].

Currently, it is stated that prolonged calming, antidepressant, and anxiolytic effects are frequently found following intravenous injections or short-term infusions of Procaine. [63,64]. Some research has shown that intravenous administration of Procaine in humans enhances blood flow to the anterior paralimbic regions and the amygdala.[65], as well as improving the hemodynamic effects on the heart. [66]. Following procaine treatment in animal models, other limbic system regions have been investigated, revealing activation of several muscarinic cholinergic receptors in the hippocampus. Numerous publications have documented Procaine's effects on various biochemical systems, including dopamine, norepinephrine, serotonin, and glutamate. Consequently, Procaine is regarded as beneficial for the investigation of the limbic system and emotions [67,68].

Recent findings indicate that procaine injection into the ventral tegmental region can inhibit the fear-conditioned avoidance response in rats and also influences hippocampal theta rhythms associated with alertness and attention [69]. The extra pharmacologic effects of Procaine are due to its metabolites. By increasing endo-cannabinoid levels, DEAE inhibits fatty acid amide hydrolase, which in turn has anti-inflammatory effects [70,71]. Because of its ester bond with ceramide, the second metabolite, PABA, has multiple functions, including antihistamine, capillary sealant, and membrane stabilizer [72-74].

The effective combination of Procaine and bicarbonate for infusion

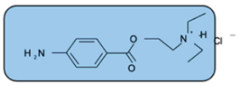
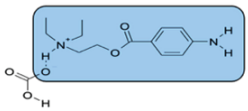
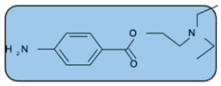
The initial mention of the combination of Procaine with alkaline salts was recorded in 1930 [24]. To amalgamate the renowned pure alkaline infusion [73] The pluripotent characteristics of Procaine were originally documented in the 1997 study known as "neural infusion therapy" [74]. Following the demonstration of significant favorable outcomes in patients with chronic pain [75], the concept rapidly acquired popularity in German-speaking nations and was integrated into textbooks on pain and brain therapy [76,77]. Glusa et al. confirmed the vasodilatory impact of Procaine-Base mixture utilizing an animal model [78]. An elevation of intracellular Procaine levels resulting from the incorporation of sodium bicarbonate [79]An expedited initial effect was also noted in animal experiments. [80,81]. The sustained administration of Procaine-Base through a medical pump exhibited remarkable outcomes in numerous severe instances of pain and inflammation [82-84]. A comprehensive analysis of over 20 years of experience with Procaine-based infusion was recently published [83].

In the osteoarthritic rat model, the anti-rheumatic and joint-protective effects of Procaine-Base following intra-articular injection were significantly superior to those of Dexamethasone [84].

The main goal of incorporating the natural buffer sodium bicarbonate was to influence the plasmatic breakdown of Procaine, as mediated by serum esterase activity. All local anesthetics exhibit comparable properties of general distribution and ionization. The significance of these attributes lies in their impact on voltage-

dependent sodium channels. The uncharged Procaine molecule acts as the transport structure that enables permeation. The ionized form, Procaine-H+, attaches to the sodium channel receptor, consequently blocking impulse propagation. The pH value of the solution and the terrain can affect the ionized and non-ionized forms of Procaine [85].

Table. 2: *The main differences between Procaine and Procainium-hydrogen-carbonicum (ProcCluster®)*

Procaine hydrochloride 	**ProcCluster®**  **marked area corresponds to the active substance**	**Procaine** 
highly water-soluble	highly water-soluble	highly soluble in organic solvents
acidic (pH value approx. 4)	approximately physiological pH value (≈ 7.6)	basic
ionic	outwardly neutral (inner salt)	unloaded
low absorption	permeation and penetration capable	membrane-permeable
hydrophil	ambiphil (hydrophil und lipophil)	hydrophob
only parenterale application	application (parenteral, oral, nasal, dermal, inhalative, buccal)	is not administered as a pure substance

Source: own elaboration

Table 2 shows that a shift in pH can significantly affect solubility and membrane permeability. Consequently, the incorporation of an alkaline addition alters the correlation between the mode of transport and the mode of action. At a low pH value (<6), just 0.1% of Procaine was detected in the lipid-soluble form [40]. Moreover, varying amounts of sodium bicarbonate can affect intracellular pH [86].

It was hypothesized that, under alkaline conditions, the conversion of Procaine to para-aminobenzoic acid (PABA) and diethylaminoethanol (DEAE) would be significantly diminished. Contrary to this idea, it is posited that, following intravenous injection of Procaine-Base, it is diluted in the blood of prominent capillaries, resulting in a rapid decrease in pH, ultimately returning to normal physiological values. Furthermore, the pulmonary circulation will induce a respiratory compensation for alkalosis. The slowing of Procaine degradation can be explained as follows: The aforementioned pH-dependent dissociation change will lead to elevated levels of the more effectively penetrating transport forms. This is characteristic of all local anesthetics, with 3-40% of the released base present, depending on the anesthetic agent's pKa. In addition to the steady-state distribution, the distribution rate is also significant. The distribution speed is the limiting factor, indicating that membrane diffusion is the rate-determining step[87]. The distribution is directly dependent on the drug's lipophilicity. Altering the pH modifies the lipophilic characteristics. An increased concentration of free base correlates with enhanced penetration, which is readily accessible to adjacent tissue and is not readily degraded by serum esterase [40].

Procaine Base Infusion Methodology

A test application of one drop of 1% Procaine into the conjunctiva is recommended if prior information regarding Procaine tolerance is unavailable before the infusion. The patient may experience a transient, mild burning sensation (attributable to HCl) and mild acute erythema (resulting from increased blood flow). Additionally, numbness is expected. Please refrain from administering parenteral infusions if the burning sensation persists for an extended period. It is imperative to emphasize that only Procaine-HCl with pharmacological authorization for intravenous administration and devoid of preservatives (e.g., parabens) should be used.

It is advisable to initiate treatment with a carrier solution of 250 to 500 ml, a dosage of 50-100 mg Procaine-HCl, and 20 ml of diluted sodium hydrogen carbonate (8.4%). Simultaneously, a comparable electrolyte solution may be used to prevent hypernatremia instead of the isotonic sodium chloride solution, which has been used for many years. The infusion lasts approximately 45 to 60 minutes. The Procaine-Base infusion should be titrated at a rate of 50 mg Procaine-HCl and 10 ml sodium bicarbonate

(8.4%) until the desired therapeutic effect is achieved. The maximum permissible dosage of Procaine-HCl for an individual of normal weight is 300 mg (refer to dosing table 3). It is recommended that, for individuals with cardiovascular risk factors, a monitoring technique (e.g., single-canal electrocardiogram/oximetry) be used when the concentration of Procaine-HCl exceeds 300 mg. It is suggested that a 30-minute observation period be maintained after the treatment. After infusion, the patient should refrain from operating a motor vehicle for approximately 1 hour. To prevent the degradation of unstable Procaine, the Procaine-base mixture should be used within 2 hours.

In the absence of prior acid-base diagnostics, the Procaine-Base infusion should not be delivered more than 3 times weekly, with at least 1 day of rest between treatment sessions. A series of 6 to 10 infusions has been authorized based on the medical situation.

Table 3a: *Dosage table for Procaine 1% (modified acc. to Oettmeier et al 2019)*

Procaine dosage 1 %	Sodium-hydrogencarbonate dosage 8.4 %	Sodium chloride 0.9 %	Total volume
100 mg = 10 ml	20 ml	500 ml	530 ml
200 mg = 20 ml	40 ml	500 ml	560 ml
300 mg = 30 ml	60 ml	500 ml	590 ml
400 mg = 40 ml	80 ml	500 ml	620 ml
500 mg = 50 ml	100 ml	500 ml	650 ml

Table 3b:*Dosage table for Procaine 2% (modified acc. to Oettmeier et al 2019)*

Procaine dosage 2 %	Sodium-hydrogencarbonate dosage 8.4 %	Sodium chloride 0.9 %	Total volume
100 mg = 5 ml	20 ml	500 ml	525 ml
200 mg = 10 ml	40 ml	500 ml	550 ml
300 mg = 15 ml	60 ml	500 ml	575 ml
400 mg = 20 ml	80 ml	500 ml	600 ml
500 mg = 25 ml	100 ml	500 ml	625 ml

The standard haematological indicators of inflammation, including the erythrocyte sedimentation rate and C-reactive protein (CRP), are expected to increase following a series of Procaine-Base infusions. Patients often report a significantly enhanced mood and improved overall condition after 6 to 10 treatments. In cases of a favorable response to treatment (termed "responders," occurring in approximately 80% of patients), it is recommended, particularly for chronic conditions, to continue long-term therapy with an adequate dosage at extended intervals, such as once or twice monthly [34,35,36].

General experiences with Procaine-Base-Infusion

The alleged hypersensitivity to Procaine, referred to as “para-group allergy” in older texts, has not yet been substantiated [88,89]. A meta-analysis of critical data during Procaine-Base infusions in 5,698 patients, which included comprehensive documentation of vital parameters during and after the injection, did not reveal any statistically significant differences between the primary groups [90]. The readings remained exceptionally stable, even at elevated Procaine concentrations. Most recorded treatment protocols consisted of medium concentrations of Procaine (100-

300 mg) and sodium hydrogen carbonate (8.4%, 20-60 ml), which are considered standard everyday practice. High concentrations of Procaine (exceeding 500 mg) and sodium bicarbonate (8.4%, exceeding 100 ml) resulted in a marginal increase in average blood pressure. Moreover, it is essential to note that the blood pressure recorded did not exhibit any significant variation at 15 or 30 minutes after the infusion.

Despite administering Procaine treatment infusions in nearly 2 million cases in accordance with the established protocol, we have not documented a single case of chronic or severe adverse effects in our clinics and outpatient facilities. The absence of any reports of severe allergic emergencies further substantiated Becke's conclusions regarding the substantial therapeutic safety of Procaine. We have not documented a single instance of long-term or severe adverse effects in our clinics and outpatient facilities, despite administering Procaine treatment infusions in nearly one million cases in accordance with the established protocol. Becke's The absence of any reports of severe allergic emergencies further supported Becke's conclusions regarding the substantial therapeutic safety of Procaine. [58]. Heart palpitations (6%) and excessive perspiration (5%) are occasionally reported by individuals. Patients taking calcium antagonists, nitro compounds, and beta-blockers appear to be more susceptible to these adverse effects, according to our observations. In such cases, the negative isotropic and negative rhythmotropic properties of Procaine are overshadowed by the reflecting and over-segmental disinhibitory effects of anesthesia. As anticipated, approximately 6% of patients may experience a transient decrease in blood pressure and vasovagal syncope during the procedure. These symptoms subside within a few minutes, particularly when the infusion rate is reduced [34,63].

A subset of patients (5%) experiences sleep disturbances and a general sensation of hyperactivity that persists for up to 1 day post-infusion, without a reduction in physical labor capacity. Mild dizziness and transient migraines were reported by approximately 4.5% of the treated individuals. In accordance with the holistic principles of brain therapy, such reactions may manifest as the "first reaction" (Hering's effect), particularly during the initial infusions [1] and homeopathy [91].

The main Indications of Procaine-Base-Infusions

The wide range of therapeutic actions of Procaine, when combined with an alkaline addition, accounts for the extensive range of medical indications (Table 4).

Table 4: *Main indications of Procaine-Base-Therapy*

Infection (acute and chronic)	**flu-like symptoms, Influenza A, Herpes simplex, Aspergillusniger, post COVID-19 and post vaccination COVID-19 syndrome, Lyme disease, Herpes zoster**
Pain Management (acute and chronic)	migraine, headache, activated osteoarthrosis, postoperative pain, Radicular syndrome, pseudo-radicular syndrome, Sudeck's syndrome, Sudeck's syndrome, early stage of algodystrophy, multiple arthralgia, Fibromyalgia
autoimmune Diseases	Scleroderma, Lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, Hashimo-to's and Crohn's disease, neurodermatitis, multiple sclerosis, algodystrophy, all kinds of neuralgia, ulcerative colitis, polymyalgia rheumatica,
Complementary On-cology	as an essential part of complementary oncology and immunotherapy,pain management of cancerous diseases, to reduce side effects of tumor-destructive treatments (Chemo-therapy, radiation), and prevention of recurring as an essential part of complementary oncology and immunotherapy, Oncology
Internal Medicine	periphery circulatory disorders, constipation, dysmenorrhea, Clinical and para-clinical hints for tissue acidosis, osteoporosis,

Source: *own elaboration*

Absolute contraindications to the infusion are exceedingly rare, provided that both the therapist and their personnel are adequately trained in the methodology and have experience administering parenteral Procaine. It is suggested that the procaine base infusion be avoided or that only minimal doses be administered in cases of neurosis, psychosis, or hypersensitivity to Procaine with ambiguous compliance. Additionally, it is essential to check the manufacturer's product information for sodium bicarbonate and Procaine.

Status: Procaine-Base-Infusion adapted to the acid-base-balance

The author Saha reported that three of 13 patients experienced clinical manifestations of metabolic alkalosis as the eighth most common side effect after 7 Procaine-Base infusions with progressively escalating concentrations, culminating at 300 mg Procaine-HCl and 120 ml of 8.4% sodium bicarbonate.[92]. Base excess (BE) measured by arterial blood gas was always more than plus two before and after these infusions, confirming metabolic alkalosis. The Procaine-Base infusion approach prevents the need for daily sodium bicarbonate treatment at such high doses. Only patients with proper acid-base equilibrium can use this daily medicine. The body's buffer system must not overflow. Increasing numbers of people have metabolic alkalosis and impaired compensatory capacity for acid-base balance. This occurs in cases of advanced malignancy, hepatic insufficiency, and colon putrefactive dysbiosis. Antacids, alkaline powders, loop diuretics, and high salt intake worsen acid-base imbalance to alkalosis[93,94]. For the assessment of acid-base equilibrium, it is recommended that the traditional blood gas analysis EPOC[95]. The test provides precise information regarding base excess and specifies the exact quantity of base required. Metabolic alkalosis may also arise in the context of hyponatremia, hypokalaemia, and elevated ammonia concentrations in EDTA plasma.

Metabolic acidosis is most observed in instances of inflammation, cardiac and renal failure, rheumatic conditions, and pain-related disorders[96]. These individuals require an elevated buffer base and should be administered sodium bicarbonate between 60 and 120 ml (8.4% solution) alongside Procaine. Unlike metabolic alkalosis, as seen in Figure three below, there is minimal or no need for supplementary base treatment. In this instance, we provide only Procaine-HCl infusions, with a carrier solution. Furthermore, we recommend administering 3-5 ampules of L(+)-lactic acid. Alternatively, the newly formulated Procainium-hydrogen-carbonicum compound, available as a ready-to-use rapid infusion (0.1-0.3%), is advised[97].

Analyte	Result	Reference range	Critical range	Reportable range	Status
pH	7.467	7.350 - 7.450	5.500 - 9.000	6.500 - 8.000	High
pCO2	39.4 mmHg	35.0 - 48.0	4.0 - 251.0	5.0 - 250.0	
pO2	57.0 mmHg	83.0 - 108.0	4.0 - 751.0	5.0 - 750.0	Low
Na+	142 mmol/L	138 - 146	84 - 181	85 - 180	
K+	4.1 mmol/L	3.5 - 4.5	0.5 - 13.0	1.5 - 12.0	
Cl-	106 mmol/L	98 - 107	64 - 141	65 - 140	
Ca++	1.19 mmol/L	1.15 - 1.33	0.00 - 5.00	0.25 - 4.00	
TCO2	28.4 mmol/L	22.0 - 29.0	4.0 - 51.0	5.0 - 50.0	
Glu	103 mg/dL	74 - 100	19 - 701	20 - 700	High
Lac	0.76 mmol/L	0.36 - 0.75	0.00 - 21.00	0.30 - 20.00	High
BUN	24 mg/dL	8 - 26	2 - 121	3 - 120	
Urea	8.6 mmol/L	2.9 - 9.3	0.7 - 43.2	1.1 - 42.8	
Crea	1.02 mg/dL	0.51 - 1.19	0.00 - 16.00	0.30 - 15.00	
Hct	34 %	38 - 51	9 - 76	10 - 75	Low
cHgb	11.7 g/dL	12.0 - 17.0	2.3 - 26.0	3.3 - 25.0	Low
cHCO3-	28.4 mmol/L	21.0 - 28.0	0.0 - 86.0	1.0 - 85.0	High
BE(ecf)	4.7 mmol/L	-2.0 - 3.0	-31.0 - 31.0	-30.0 - 30.0	High
BE(b)	4.4 mmol/L	-2.0 - 3.0	-31.0 - 31.0	-30.0 - 30.0	High
cSO2	90.9 %	94.0 - 98.0	-1.0 - 101.0	0.0 - 100.0	Low
BUN/Crea	23.6 mg/mg	12.0 - 20.0	0.1 - 400.1	0.2 - 400.0	High
Urea/Crea	95.5 mmol/mmol	48.5 - 80.8	0.4 - 1615.8	0.8 - 1615.4	High

Figure 3: *Findings of metabolic alkalosis. Source: own elaboration based on the system EPOC, Siemens HealthCare AG.*

Based on the BE results of the acid-base test, we recommend the following adjustment of bicarbonate quantity for the infusion (Table 5):

Table 5: *Adjustment of the sodium-bicarbonate amount for the Provaine base infusion according to the blood gas analysis*

Base excess (mmol/l)	**> 0**	**-1 - 0**	**-2 - -1**	**< - 2**
Bi-carbonate (mmol/l)	> 25	22 - 25	19 - 22	< 19
Amount of 8.4% Bicarbonate solution (ml)	20	40	60	80

To assess the efficacy of Procaine-Base infusion, it is advisable to review the thoroughly documented case reports in the article by Oettmeier et al.[129]

Procaine infusion and neural therapy with Procaine

In neural therapy, local anaesthetics containing Procaine are used not merely as pharmacological agents but as regulatory instruments within the autonomic and somatic nervous systems(175-185). Their diagnostic and therapeutic impact arises from the profound regulatory and plastic properties of neural networks, as extensively described in the works of Nazlikul, Fischer, Oettmeier, and many others[31,118,119,126,136,144,145,146,148,153,156,175-180, 818-185]. Over the past 100 years, clinical experience has demonstrated that Procaine injections serve as precise neuromodulatory interventions, capable of influencing segmental, suprasegmental, and interference-field-related reflex patterns.

Targeted mechanical stimulation by the needle, combined with short-term engram deletion induced by Procaine, initiates a functional "reset" within the autonomic network. This momentary deactivation of pathological excitation patterns enables reorganization of neuronal signalling pathways and normalization of microcirculatory dynamics(174-181). As Speransky emphasized, once the pathological loop is interrupted, the organism can reorganize itself in response to new internal and external information—a process he called self-eco-organization. This concept has been repeatedly validated in clinical practice, particularly in the treatment of chronic pain, autonomic dysregulation, neurogenic inflammation, and functional disorders [98-105].

Pathologically stored engrammatic excitability, especially in the sympathetic chain, spinal reflex arcs, nociceptive pathways, and supraspinal modulation centres, can be reduced or normalized through targeted Procaine injections(182-185). The therapeutic effect therefore far exceeds the short pharmacological duration of anaesthesia; instead, it represents a sustained shift in autonomic coherence and microcirculatory regulation[145, 146, 148, 149, 99 ,100 ,101, 102, 103, 175-180, 181-185].

From the perspective of experienced clinicians—including those in the field of Neural Therapy, who constitute the largest global group of physicians working daily with Procaine and Lidocaine—the synergy between injection-based neural therapy and systemic Procaine-based infusions is particularly valuable (177-185). These practitioners possess unparalleled empirical insight into the broader regulatory behaviour of these substances, far beyond their classical use as anaesthetics[104, 105, 106, 107, 108, 175-180].

It is therefore the precise position of the authors that intravenous Procaine-based therapy and neural therapeutic injections must not be regarded as competing or mutually exclusive modalities (172-185). On the contrary, especially in chronic, complex, and therapy-resistant conditions, the combination of both techniques yields a more profound regulatory impact. High-dose Procaine-base infusions modulate systemic inflammatory thresholds, autonomic tone, and microcirculatory patterns, thereby preparing the terrain for more targeted neuromodulation through segmental or interference-field injections [109-113, 178-785].

Both procedures can be applied sequentially or in combination, depending on the patient's regulatory capacity. When integrated, they reflect the most advanced level of therapeutic practice derived from a century of Neural Therapy—uniting systemic modulation with precise neuro-regulative intervention, in alignment with the contemporary research of Nazlikul and Fischer that underscores autonomy, plasticity, and self-regulation within the human organism[110, 111, 112, 113, 171-180, 171-185].

Is Procaine infusion comparable with Lidocaine?

The local anaesthetic lidocaine belongs to the amide group and is primarily metabolized in the liver. It has proven effective for local and regional anaesthesia for decades. For the first time, intravenous lidocaine was used to support anaesthesia. It was found that IV lidocaine administration can be used as an adjunct to aesthetics and has analgesic effects[114]. A randomized, double-blind study of 20 patients after cholecystectomy showed that a continuous low-dose lidocaine infusion (beginning 30 minutes before surgery and continuing for 24 hours postoperatively) significantly reduced postoperative pain. The lidocaine group had significantly lower pain scores on the first postoperative day and required fewer opioid analgesics than the placebo group. No side effects occurred, and measured lidocaine blood levels were within the therapeutic range (1–2 µg/ml)[115,175,179]. Different kinds of chronic and neuropathic pain were successfully treated by Lidocaine infusion. A controlled study investigated the effect of IV lidocaine on painful diabetic neuropathy. The authors reported that lidocaine infusions significantly reduced subjective neuropathic pain, although objective signs of neuropathy (e.g., sensory disturbances) remained unchanged[116].

Case series of 23 patients with herpes zoster who received a weekly infusion of 100 mg lidocaine for four weeks. Pain intensity, measured using the Numerical Rating Scale (NRS), decreased significantly after the first treatment and continued to decline with each subsequent session[117]. A Chinese case series reported on five organ transplant recipients with treatment-resistant herpes zoster neuralgia. After 2–3 lidocaine infusions (5 mg/kg over 1.5 hours), all patients reported significant pain relief, which persisted even after six months. Side effects were mild and transient[118,175]. A randomized, double-blind study of 42 patients with herpes zoster neuralgia showed that weekly lidocaine infusions (3 mg/kg over 1 hour) for four weeks resulted in significant pain reduction [119].

The second field of use of Lidocaine intravenously is cardiology. The first clinical study of lidocaine's antiarrhythmic effects showed that IV lidocaine can effectively suppress ventricular arrhythmias (e.g., ventricular premature beats and tachycardias). With continuous infusion over several days, ventricular arrhythmias could be controlled in the treated patient group without serious side effects. This study established lidocaine as an important intravenous antiarrhythmic, particularly for acute ventricular arrhythmias in the context of infarction[120]. A randomized study on the prophylactic use of lidocaine in acute myocardial infarction. Prophylactic IV lidocaine has been reported to significantly reduce the incidence of primary ventricular fibrillation (ventricular fibrillation) after myocardial infarction. These acutely life-threatening arrhythmias occurred significantly less frequently in the lidocaine group, suggesting a potential survival benefit in the early phase[121]. Both Procaine and lidocaine have overlaps and distinct uses in everyday clinical practice. However, the diversity of their pharmacological properties allows Procaine to have a much broader range of indications.

DISCUSSION: The present systematic review highlights that intravenous Procaine and Procaine–based infusions are far more than historical curiosities of neural therapy; they represent a pharmacologically and clinically underutilized option in an era marked by an unprecedented rise in chronic, degenerative, and multimorbid diseases [172-180].

When the synthesis of Procaine in 1905 and the later introduction of lidocaine as an amide-type local anaesthetic in the mid-20th century are viewed against today's epidemiological backdrop, a striking paradox becomes evident: two substances with well-documented pleiotropic actions have remained confined mainly to narrow indications (local anaesthesia, antiarrhythmic use, adjuvant pain treatment), while global health systems struggle with exploding costs and limited effectiveness of purely symptomatic polypharmacy in chronic disease management [175, 176, 178, 180-185].

Procaine beyond local anaesthesia: regulation of inflammation, circulation, and degeneration

The data summarized in this review clearly show that Procaine exerts a broad spectrum of systemic effects that extend far beyond transient sodium-channel blockade and local anaesthesia. Experimental and clinical observations demonstrate anti-inflammatory, vasodilatory, sympatholytic, broncho-spasmolytic, anti-oxidative, geroprotective, and even epigenetically mediated anti-tumour properties.

Multiple studies cited in this work describe:

- Improvement of microcirculation and coronary perfusion
- Reduction of rheumatic inflammation and joint damage
- Modulation of MAPK signalling, cytokine expression (e.g., IL-6), and immune responses

- Partial inhibition of DNA methyltransferases and restoration of tumour suppressor gene function
- Suppression of proliferation and migration of various cancer cell lines in vitro
- Reduction of viral replication (e.g. SARS-CoV-2, influenza) and antifungal effects

Taken together, these findings support the view that Procaine is a regulatory modulator, acting at the interface of the nervous system, vasculature, extracellular matrix, immune system, and genomic control.

Its classical use within neural therapy – local, segmental, and systemic – already anticipated this broader regulatory paradigm[178, 179, 180, 181-185].

Clinical relevance in an era of chronic disease and multimorbidity

The prevalence of chronic pain, cardiovascular disease, autoimmune disorders, neurodegeneration, and malignancy has risen dramatically over the last decades. At the same time, the standard response of conventional medicine has often been to add more and more drugs to increasingly complex medication regimens, with well-known consequences: interactions, adverse effects, reduced adherence, and a growing economic burden[175-180].

In this context, the profile of Procaine and Procaine–based infusion is notable for several reasons:

1. Multimodal efficacy across pain, inflammation, vascular dysfunction, autoimmunity, oncology, and psycho-vegetative dysregulation.

2. **Favourable safety** due to rapid plasma breakdown and the absence of significant long-term toxicity in large case series and meta-analyses.

3. Potential cost reduction, as the same intervention may improve multiple symptom complexes and thereby diminish the need for numerous symptomatic drugs (e.g., opioids, NSAIDs, antidepressants, antiarrhythmics).

4. Synergy with neural therapy: intravenous Procaine–based infusions can lower pain and inflammation thresholds, while segmental and interference-field injections address specific neuro-modulatory triggers.

Given this profile, it is reasonable to hypothesize that broader, structured use of Procaine – similar to the established systemic use of lidocaine in neurology and cardiology – could significantly reduce drug consumption and healthcare expenditures, particularly among complex chronic patients.

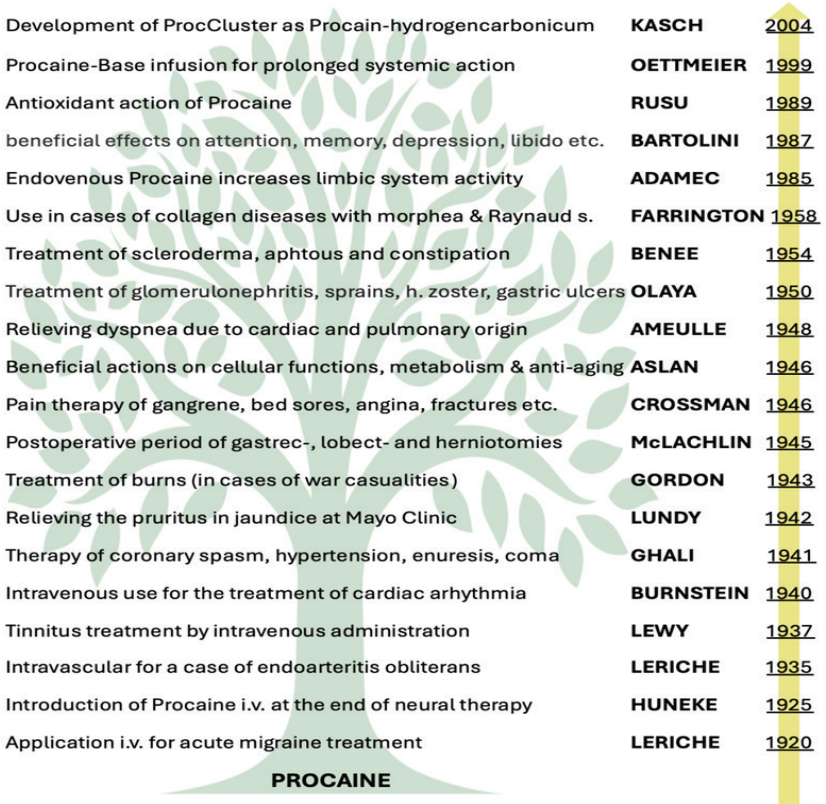


Figure 5: *The endovenous "Procaine tree" illustrates the milestones of its utilization and evolution during the past century*

Lidocaine and Procaine – tradition, overlap, and blind spots

Lidocaine has been widely investigated and accepted for systemic use in peri- and postoperative pain, neuropathic pain, and ventricular arrhythmias.

Procaine, by contrast, despite its more extended history and extensive empirical use, has remained marginalized mainly outside the field of neural therapy and a few specialized centres [175,180].

The available data do not justify this imbalance. On the contrary, Procaine's:

- ester-type metabolism with rapid hydrolysis,
- vasodilating rather than vasoconstrictive action,
- broad geroprotective, epigenetic, and matrix-modulating effects,

Suggest that Procaine is at least as deserving of systematic clinical exploration as lidocaine – and possibly better suited as a long-term regulation-modulating agent in chronic disease states.

The historical tendency of academic medicine to constantly pursue the "newest molecule" represents a structural bias: older, inexpensive, off-patent substances with pleiotropic regulatory actions receive less scientific attention—not due to a lack of efficacy, but because they are economically unattractive. Procaine and lidocaine are exemplary victims of this dynamic. This historical trajectory and the resulting neglect of well-established regulatory therapies are clearly visualized in Figure 5, where the endovenous "Procaine tree" illustrates the milestones, expansions, and clinical evolution of Procaine-based therapy over the past century.

The need for modern, large-scale clinical research

Although this review collates over a century of experimental and clinical data, including case series, controlled trials, mechanistic studies, and observational research, the evidence base still suffers from heterogeneity in design, dosing, and indication[178, 179, 180].

From a contemporary perspective, several clear research priorities emerge:

1. **Randomised controlled trials** of Procaine–based infusion in chronic pain, cardiovascular diseases, autoimmune disorders, and early neurodegenerative conditions.

2. **Comparative effectiveness studies** of Procaine versus lidocaine and versus the standard of care in pain therapy and cardiology.

3. Oncological trials evaluating Procaine as an adjuvant to reduce chemo- and radiotherapy toxicity and to modulate tumour biology (epigenetic, anti-inflammatory, and immune effects).

4. **Health-economic analyses** quantifying potential reductions in polypharmacy, hospitalisation days, and indirect costs (loss of productivity, disability).

5. **Longitudinal geriatric studies** assessing Procaine as a geroprotective intervention that targets multiple hallmarks of ageing simultaneously.

Such studies are not only scientifically justified by the mechanistic plausibility and clinical observations summarised here, but also ethically warranted in light of the global burden of chronic diseases and the limitations of current therapeutic strategies.

Procaine as a bridge between neural therapy and pharmacology

A central message of this work is that Procaine should no longer be viewed solely as a local anaesthetic used in neural treatment or as an antiarrhythmic agent, but rather as a bridge substance between regulatory medicine and conventional pharmacology.

Intravenous Procaine–base infusion and targeted procaine injections in neural therapy are complementary, not competing procedures.

In combination, they have the potential to:

- reset dysregulated autonomic and central networks,
- restore trophic and circulatory balance,
- break chronic pain–inflammation cycles,
- improve patients' quality of life and functional capacity,
- Moreover, ultimately, reduce the dependence on multi-drug regimens.

In conclusion, given its pleiotropic mechanisms, long clinical history, and favourable safety profile, Procaine deserves a renewed and systematic place in 21st-century medicine. If integrated wisely and studied rigorously, Procaine and lidocaine could become key tools for addressing the unmet needs of patients with complex chronic diseases – and for mitigating the growing economic strain on healthcare systems worldwide.

Conclusion and Outlook

More than 100 years after the first empirical use of intravenous Procaine, this therapeutic approach has evolved from a clinical curiosity into a method with substantial, well-documented regulatory potential. Today, it has become an established component of pain medicine, neurovegetative regulation, rehabilitation, and bioregulatory medicine in numerous hospitals and outpatient practices. Although a considerable body of scientific evidence substantiates the systemic mechanisms of Procaine—particularly its anti-inflammatory, vasodilatory, sympatholytic, antioxidant, epigenetic, and microcirculatory effects—its broad spectrum of indications and individualized application require further structured investigation.

The metaphor of the "Procaine Tree" vividly illustrates the historical evolution and multidimensional clinical expansion of Procaine therapy. Emerging from a single scientific root in the early 20th century, Procaine has branched into multiple therapeutic domains: pain modulation, autonomic regulation, cardiovascular support, immune balance, neurodegeneration, oncology, and psychosomatic medicine. These branches continue to proliferate as clinical experience and fundamental research uncover new mechanistic insights and therapeutic opportunities.

In the context of the dramatic global rise of chronic, degenerative, and multimorbid conditions, intravenous Procaine therapy offers physicians a multimodal, low-risk, and cost-effective tool capable of addressing several pathological layers simultaneously—nervous, vascular, immune, metabolic, and epigenetic. This stands in stark contrast to the conventional approach of escalating polypharmacy, which often treats isolated symptoms rather than underlying dysregulation and frequently leads to drug interactions, diminished quality of life, and escalating healthcare expenditures.

Based on the authors' and many international colleagues' long-standing clinical experience, intravenous Procaine appears capable of making a meaningful contribution to a modern therapeutic paradigm in which regulation, resilience, and functional restoration replace the narrow symptom-suppression model. Observational data and day-to-day clinical practice consistently show that Procaine-based therapy can reduce the need for chemical pharmaceuticals—opioids, NSAIDs, antidepressants, antihypertensives, antiarrhythmics—by improving underlying regulatory processes that give rise to these symptomatic burdens. This has important implications not only for patient safety and quality of life, but also for reducing the economic strain on healthcare systems worldwide.

For these reasons, the authors strongly support the need for broader, systematic, and interdisciplinary research in the coming decade, including randomized trials, mechanistic studies, and health-economic analyses. Such efforts would not only clarify optimal dosage regimens and specific indications, but also pave the way for integrating Procaine therapy into evidence-based guidelines for chronic diseases—conditions for which current treatment strategies often fall short.

In conclusion, intravenous Procaine, viewed through the lens of its century-long evolution and expanding scientific foundation, must be regarded as a high-value regulatory intervention with global relevance. Its integration into contemporary medical practice represents not an alternative to conventional pharmacology but an urgently needed complement—bridging the gap between biological regulation, neural therapy, and modern evidence-based medicine. Given the magnitude of current health challenges, the systematic exploration and clinical implementation of Procaine-based therapy is not only scientifically justified but, in the authors' view, an ethical imperative for the future of universal human health.

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The authors declare that they have no conflicts of interest related to this publication.

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Authors' Contributions

All authors contributed significantly to the conception, writing, and refinement of this manuscript.

The order of authorship reflects equal intellectual contribution.

- R. Oettmeier and H. Nazlikul contributed equally to the conceptual design, structure, and overall development of the manuscript, including the historical analysis, clinical integration, and systemic interpretation of intravenous Procaine therapy.
- L. Bibiana Pinilla-Bonilla provided expertise on the pharmacological properties and clinical applications of Procaine, supported by extensive literature review and practical experience in neural therapy. She contributed key sections related to pharmacodynamics, clinical indications, and methodological considerations.
- F. Gülçin Ural Nazlikul focused on literature review and scientific analysis regarding the autonomic nervous system, neural therapy mechanisms, lidocaine infusion, and neurovegetative regulation. She contributed substantially to the discussion section and strengthened the manuscript's scientific depth and coherence.
- U. R. M. Reuter made significant contributions to the sections addressing the historical evolution of Procaine use, infusion methodologies, and therapeutic indications, and performed a comprehensive evaluation of the relevant literature.

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