
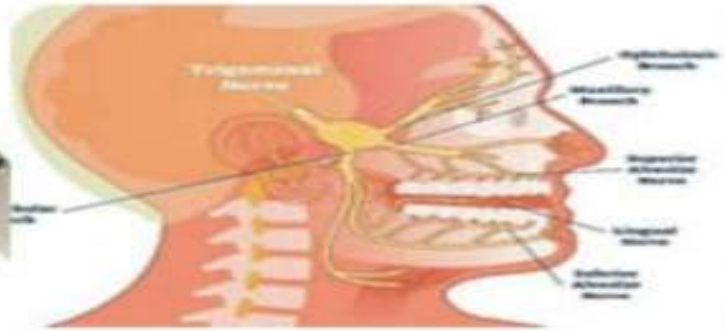
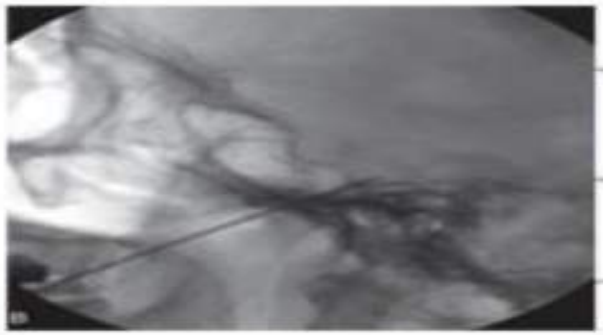
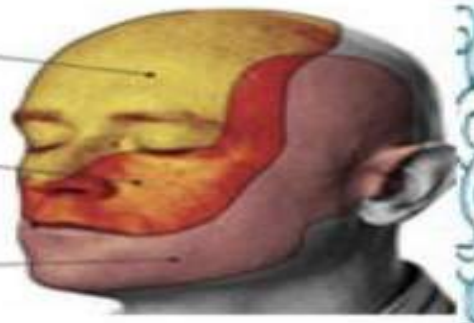

درمانهای جدید در نورالژی عصب سه قلو

Recent Advances inTrigeminal Neuralgia

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Defination

- The International Association for Study of Pain (IASP) has defined TN as “sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve.”2 A variety of triggers such as shaving, chewing, drinking, talking, smiling, brushing the teeth, washing the face, and encountering a breeze may initiate the pain of TN. Usually, pain resolves completely between the attacks. It usually does not occur when the person is asleep.
- Rapid spreading to other division, bilateral involvement, or simultaneous involvement of other nerve suggests a secondary disease such as multiple sclerosis (MS) or expanding cranial tumor.
- Epidemiological studies show increased anxiety and depression, with increased risk of suicide.1 This highlights the importance of prompt diagnosis, investigations and treatment.

Theories Described for Trigeminal Neuralgia

- Trigeminal Convergence Projection Theory The continuous nociceptive inputs that are received from the head and neck converge in the spinal trigeminal nucleus. The neurotransmitters released from the nucleus excite the second-order neurons which gives rise to a type of chronic neuropathic pain.8
- Bio resonance Hypothesis This is a new hypothesis which proposes that if the vibration frequency of a structure near the trigeminal nerve becomes close to its natural frequency, the resonance of the trigeminal nerve occurs. This can cause abnormal transmission and results in pain.9
- Ignition Hypothesis Injury to the trigeminal afferent neurons in the REZ makes the axons hyperexcitable and leads to synchronized discharge activity.10

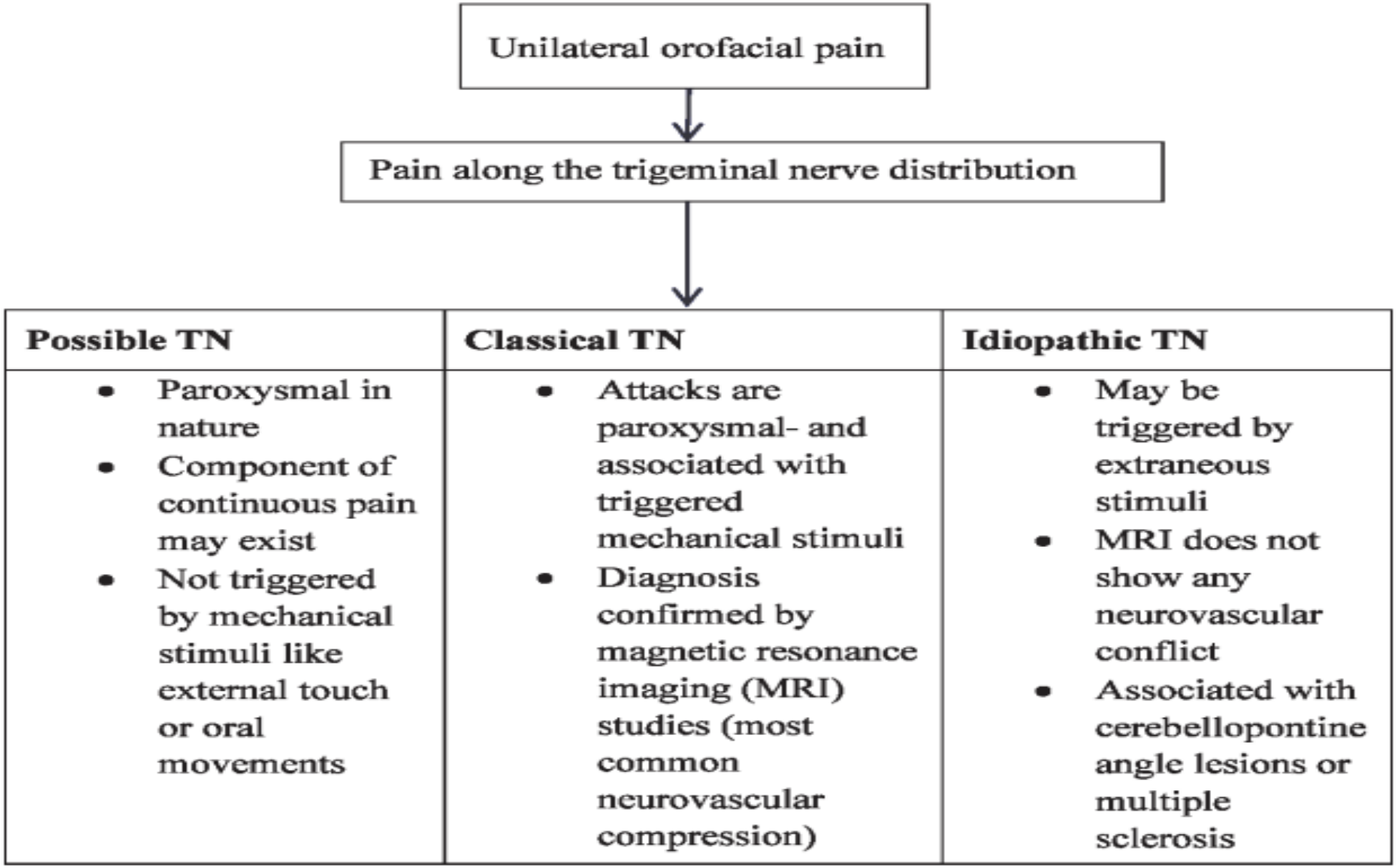

Fig. 1 New classification and diagnostic flowchart of trigeminal neuralgia (TN).

Epidemiology

- The life time prevalence of TN is estimated to be 0.16%–0.3%,2 3 while the annual incidence is 4–29 per 100000 person- years.4–6 It is more prevalent in women than in men (F:M ratio 3:2).5 7
- The incidence increases with age, with a mean age of onset of 53–57 years and range of 24–93 years in adult series.1 7
- Further- more, a recent paediatric headache clinic of 1040 identified five children in the age range 9.5–16.5 years with TN.8

Differential diagnosis of trigeminal neuralgia

Dental causes	**•Dental caries** **•Pulpitis** **•Dental sensitivity** **•Periodontal disorders** **•Pericoronitis** **•Cracked tooth** **•Alveolar osteitis**
Sinus causes	**•Maxillary sinusitis**
Salivary gland causes	**•Salivary stone**
Temporomandibular joint causes	**•Temporomandibular disorders**
Neuropathic pain	**•Glossopharyngeal neuralgia** **•Nervus intermedius neuralgia** **•Post-herpetic neuralgia** **•Post-traumatic trigeminal neuropathy** **•Painful trigeminal neuropathies** **•Atypical odontalgia** **•Burning mouth syndrome**
Trigeminal autonomic cephalalgias	**•SUNCT/SUNA** **•Paroxysmal hemicrania** **•Cluster headache** **•Hemicrania continua**
Other	**•Persistent idiopathic facial pain** **•Primary stabbing headache**

•SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms;

• SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Clinical differences between trigeminal neuralgia and SUNCT/SUNA

Features	Trigeminal neuralgia	SUNCT/SUNA
Predominant pain distribution	V2/V3>V1	V1>V2/V3
Severity of pain	Very severe	Very severe
Duration (seconds)	<1–120	1–600
Autonomic features	None or sparse	Prominent
Spontaneous attacks only	None or rare	40%
Refractory period	Present	Absent
Periodicity	Mostly episodic	Mostly chronic
Preventive treatment of choice	Carbamazepine or oxcarbazepine	Lamotrigine

•SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms;
• SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing;

Differential diagnosis between trigeminal neuralgia (TN) with concomitant facial pain and other trigeminal neuropathic conditions

Features	TN with concomitant persistent facial pain	Idiopathic neuropathic pain*	Neuropathic pain with identifiable cause†	Persistent idiopathic facial pain
Precipitating factor	No	No	Yes (trauma, viral, inflammatory)	No (possible stress)
Pain location	Extra/intraoral	Extra/intraoral	Extra/intraoral	Extraoral
Laterality and trigeminal distribution	Unilateral Dermatomal	Unilateral Dermatomal	Unilateral Dermatomal	Often bilateral Non-dermatomal
Pain severity	Severe–very severe	Mild to severe	Mild to severe	Mild to severe
Other sensory symptoms	None	Yes	Yes	None
Cutaneous/intraoral triggers	Present	Yes, but rare	Present	None
Effective treatments	Carbamazepine	Tricyclic antidepressants, gabapentinoids	Tricyclic antidepressants, gabapentinoids	Unclear

- *Includes persistent dentoalveolar pain, atypical odontalgia, phantom tooth pain in which the pain location is intraoral only.
- †This term mainly includes painful post-traumatic trigeminal neuropathy and post-herpetic neuropathic pain.

Pathophysiology

- The current pathophysiological hypothesis for classical TN suggests that the pain mechanisms are precipitated by a proximal compression of the trigeminal sensory root near the brainstem (root entry zone) by a blood vessel (artery or vein).
- The root entry zone is considered a vulnerable area to demyelination, due to transition from the peripheral Schwann cell myelin sheath to central myelin generated by oligodendroglia. The vascular compression may start a process of focal demyelination and remyelination,[23 24] probably mediated by microvascular ischaemic damages.[25] These changes lower the excitability threshold of affected fibres and promote inappropriate ephaptic propagation towards adjacent fibres.[26] Thus, tactile signals coming from the fast myelinated (A-β) fibres can directly activate the slow nociceptive (A-δ) fibres, resulting in the high-frequency paroxysms that characterise TN. After a few seconds, these repetitive discharges spontaneously run out and are followed by a brief period of inactivity that is called 'refractory period', where triggering actions cannot provoke pain.

Pathophysiology

- The remarkable clinical effect of sodium channel blockers in TN has suggested that an abnormal expression of voltage-gated sodium channels could also constitute an important pathophysiological correlate for both classical and idiopathic TN, which might be sodium channelopathies. Nav1.7, Nav1.3 and Nav1.8 were found to be abnormally expressed in TN and possibly responsible for rapid activation and inactivation, as well as maintenance of the action potential.[27] Over time hypersensitivity of tactile A-β fibres may lead to sensitisation of second-order wide dynamic range neurones in lamina V of the dorsal horns and the trigeminal nerve nuclei. Since these wide dynamic range neurones receive convergent information from tactile (A-β) and nociceptive (A-δ and C) fibres, their sensitisation could promote the perception of pain in response to cutaneous stimulation.

Pathophysiology

- It was previously thought that TN with concomitant continuous pain occurred because of repetitive paroxysmal attacks. However, prospective cross-sectional studies show that the concomitant continuous pain often develops with or even before the onset of the paroxysmal pain.[13] TN with concomitant persistent pain seems more prevalent in women and more often associated with sensory abnormalities than paroxysmal TN. Studies looking for impairment in trigeminal nociception have shown an abnormal nociceptive blink reflex and pain-related evoked potentials, indicating overactivation of central sensory transmission, as a potential mechanism to explain the constant facial pain of TN.[28] Furthermore, an important recently published neuroimaging study using a 3T MR imaging of the trigeminal nerve roots in patients with 'TN purely paroxysmal' and 'TN with concomitant continuous pain' showed that the trigeminal nerve root was more severely atrophic in patients with concomitant continuous pain than in those with purely paroxysmal pain. It may be due to continuous pain most likely relates to axonal loss and abnormal activity in denervated trigeminal second-order neurones.

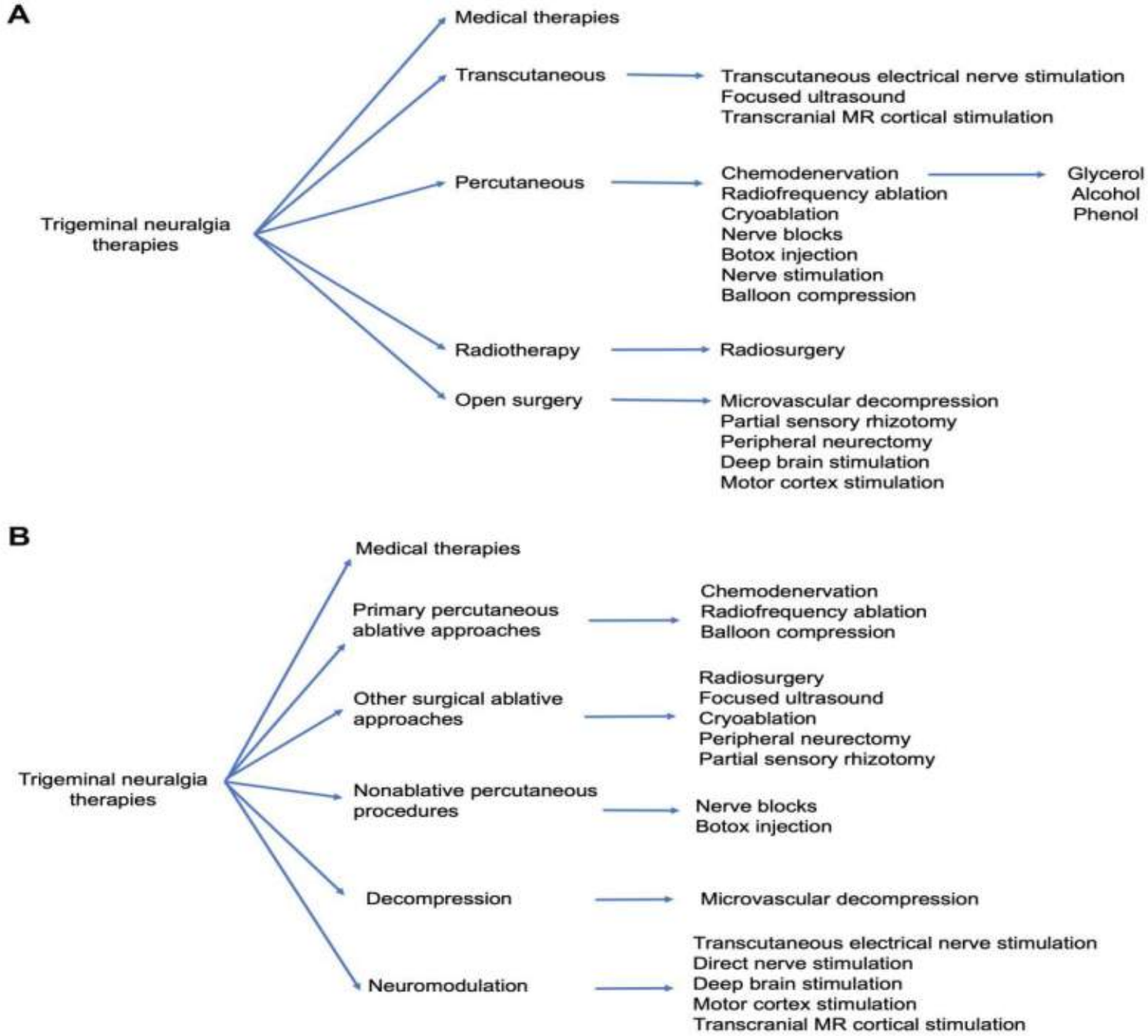

Figure 1 Schematic diagram of treatment modalities for trigeminal neuralgia. (**A**) Treatment modalities for trigeminal neuralgia grouped by operative approach. (**B**) Treatment modalities for trigeminal neuralgia grouped by mechanism of treatment.

Table 2 Summary of Transcutaneous, Percutaneous, Radiotherapy, and Open Surgical Treatment Options for Patients with Trigeminal Neuralgia

	Patient Selection Criteria	Initial Pain Relief Rates	Pain Recurrence	References
Transcutaneous				
TENS	Retractable disease without pain relief after medication	80–90% within 3 weeks	85% Reduction in pain after 3 months, but long term outcomes are not well studied	[34,52,160,209]
Focused ultrasound	Failed standard therapies, but further study is needed	Further study is needed	Further study is needed	[217,218]
Transcranial MR cortical stimulation	May be used as assessment method for cortical stimulation	50–60%	Long-term studies are lacking	[221,222]
Percutaneous				
Chemodenervation				
Glycerol	Failed medical management	70–90+%	20–40% Have pain relief	[126,128,130,131,136–138,143,144,149,152–154,156–165,181,282]
Alcohol	Failed medical management	80–90% success rate	>50% Require retreatment	[6,37,95,142,145–147,151]
Phenol	Failed medical management; end-stage cancer patients	80–90%	~40% Recurrence 1–2 years after procedure	[123,148–155]
Radiofrequency ablation	Failed medical management	75–95+%	25–50% Recurrence	[4,130,143,168,174–176,181]
Nerve blocks	Failed medical management	30–40%	Pain relief may last longer than expected based on local anesthetic's duration of action, 50–60% have sustained pain relief	[7,34,116,117,122,145–147,149,151,176,191–193,277]
Balloon compression	Failed medical management	80–90+%	15–50%	[46,124–141,143,230]
Cryoablation	Failed standard therapy	90+%	30–40%	[184,186,188]
Botox injection	Failed standard therapies	50–60%	50–60% Require second dose at 2 months, long term outcomes need further study	[63,80,83,194–205,246]
Nerve stimulation	Most commonly treating Type 2 TN in literature	40–50% but sample size is limited	Long-term outcomes need further study	[211–213]
Radiotherapy				
Radiosurgery	Patients who cannot tolerate general anesthesia or invasive procedures	Pain relief is not immediate; maximum time to pain relief is around 180 days after treatment	20–30%	[4,7,10,38,41,54,64,71,80,120,130,135,143,175,177,223–246,274]
Open surgery				
Microvascular decompression	Ability to tolerate general anesthesia and suboccipital craniectomy	>90%	~10% Underwent second operations; most recurrences within 2 years of surgery	[4,7,10,24,54,58,61–63,65,66,71,78,80,130,131,134–136,143,163,169,171,174,175,177,184,226,230,240,245,246,252–265,267–272,274,275]
Partial sensory rhizotomy	Absence of neurovascular contact on MRI	80–90%; Similar to slightly worse than MVD patients	Worse than MVD, 47% pain free at 5 years	[171,177,263,269–274]
Peripheral neurectomy	Failed medical therapy or severe medical comorbidities and unable to tolerate MVD suboccipital craniectomy	70–90+%	Up to 20%, Recurrence thought to be secondary to peripheral nerve regeneration	[276–281,283]
Deep brain stimulation	Refractory TN, excluding patients with psychogenic or factitious pain disorders, cognitive impairment, and psychiatric disease	>90%, but sample size is small	60% Require medication on follow-up, but long term outcomes are not well studied	[34,214,215,246]

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Table 2 (Continued).

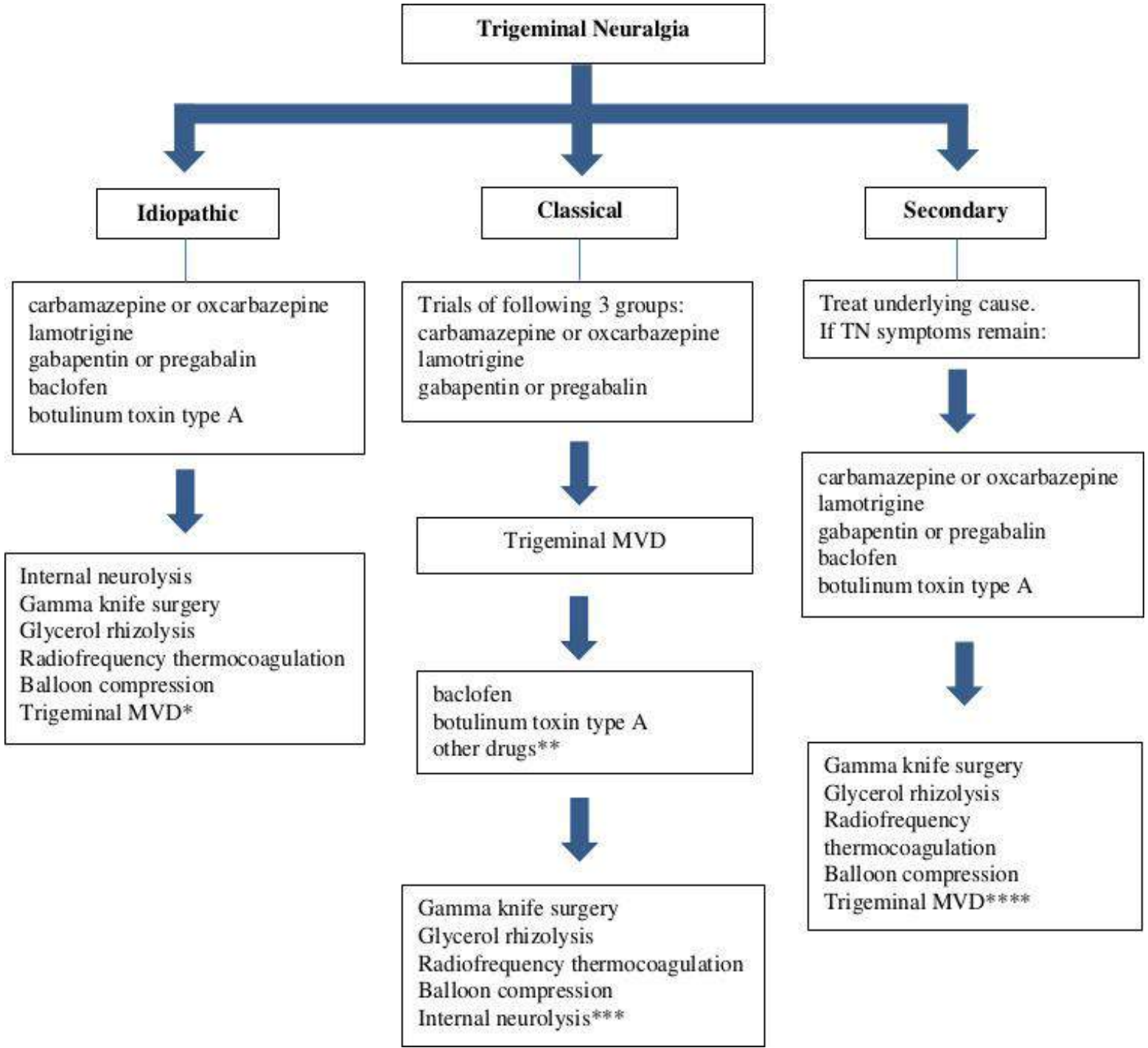
	Patient Selection Criteria	Initial Pain Relief Rates	Pain Recurrence	References
Motor cortex stimulation	rTMS may be used as an initial assessment for cortical stimulation	60–80+%, but further studies are needed	>50%, but long-term outcomes are poorly studied	[219–222]

Summary of randomised controlled trials for pharmacological treatments in trigeminal neuralgia

	Number of RCTs	Number of patients	Dose range (mg/day)	Responder rate
Carbamazepine	3	138	800–1200	68%–100%
Oxcarbazepine	1	48	600–1800	100%
Lamotrigine	1	14	200–400	85%
Gabapentin*	16	1156	Up to 3600	Reportedly similar to carbamazepine
Baclofen	1	10	30–60	70%
Botulinum toxin type A	4	178	25–100 units	68%–86%
Pimozide	1	48	4–12	100%†
Tizanidine	1	12	18	20%

Preventive treatments in trigeminal neuralgia (adapted from Bendtsen *et al* 41)

Drug	Initiating dose	Titration*	Dose range	Frequency	Tapering†	Specific side effects
Carbamazepine	200 mg	200 mg every 3 days	200–1200 mg	Two to four times per day	200 mg every 7 days	Dizziness, drowsiness, fatigue, ataxia, diplopia, nausea, cognitive slowing, hyponatraemia leucopenia, thrombocytopenia, skin reactions, abnormal liver function tests
Oxcarbazepine	300 mg	300 mg every 3 days	300–1800 mg	Four times per day	300 mg every 7 days	Dizziness, drowsiness, fatigue, nausea, ataxia, hyponatraemia, skin reaction
Lamotrigine	25 mg	25 mg for 2 weeks, 50 mg for 1 week, then increase by 50 mg every week	25–400 mg	Two times per day	50 mg every 7 days	Dizziness, drowsiness, fatigue, headache, gastrointestinal symptoms, irritability, sleep disorders, tremor, cognitive slowing, rash
Gabapentin	300 mg	300 mg every 3 days	300–3600 mg	Three times per day	300 mg every 7 days	Dizziness, confusion, fatigue, ataxia, increased risk of infection, gastrointestinal symptoms, weight gain; use cautiously with opioids
Pregabalin	150 mg	150 mg every 7 days	150–600 mg	Two times per day	100 mg every 7 days	Dizziness, confusion, ataxia, increased risk of infection, gastrointestinal symptoms, weight gain
Baclofen	15 mg	15 mg every 7 days	15–90 mg	Three times per day	15 mg every 7 days	Confusion, dizziness, drowsiness, gastrointestinal symptoms, euphoria, hallucinations
Botulinum toxin type A	25–195 units	NA	25–195 units	Every 12 weeks	NA	Transient facial asymmetry, transient bruising at injection site, transient drooling and difficulty chewing


Trigeminal Neuralgia
Idiopathic
Classical
Secondary
carbamazepine or oxcarbazepine
lamotrigine
gabapentin or pregabalin
baclofen
botulinum toxin type A
Internal neurolysis
Gamma knife surgery
Glycerol rhizolysis
Radiofrequency thermocoagulation
Balloon compression
Trigeminal MVD*
Trials of following 3 groups:
carbamazepine or oxcarbazepine
lamotrigine
gabapentin or pregabalin
Trigeminal MVD
baclofen
botulinum toxin type A
other drugs**
Gamma knife surgery
Glycerol rhizolysis
Radiofrequency thermocoagulation
Balloon compression
Internal neurolysis***
Treat underlying cause.
If TN symptoms remain:
carbamazepine or oxcarbazepine
lamotrigine
gabapentin or pregabalin
baclofen
botulinum toxin type A
Gamma knife surgery
Glycerol rhizolysis
Radiofrequency
thermocoagulation
Balloon compression
Trigeminal MVD****

Vixotrigine:

- Vixotrigine is a novel sodium channel blocker that preferentially targets higher frequencies and suppresses seizures or noxious stimuli. In an open-labeled study, vixotrigine 150 mg administered thrice daily in patients with TN was compared with placebo and showed successful pain relief in the final week of therapy.22
- The drug was administered for 21 days. There was a reduction in the number of paroxysms by 60% comparedwith only 12% in placebo, and pain severity decreased by 55% compared with placebo. The treatment failure rate was 33% with this new drug and no serious adverse event was noted.
- A multicentric prospective phase III randomized controlled trial is already underway and its results will throw further light on this drug.23

Eslicarbazepine:

- It is a third-generation antiepileptic drug belonging to the dibenzepine group. The drug targets the voltage-gated sodium channels and is currently approved as adjunct therapy for focal seizures. In a recent open-labeled trial, eslicarbazepine was administered in a dose of 200 to 1200 mg/day in patients suffering from TN.
- Around 88.9% patients had good pain relief but there was high incidence of side effects to the tune of 71%.24

Sumatriptan:

- It is a 5-hydroxytyptamine receptor (1A/B/C) receptor blocker agonist. It has been used extensively in migraine and cluster headaches with good pain relief efficacy. The drug inhibits vasodilation and demyelination near the inflamed trigeminal nerve root. The drug comes in a formulation of tablets, nasal spray, or injections. Two randomized controlled trials tested the effect of subcutaneous injection of sumatriptan 3 mg and the oral administration of 50 mg twice daily. Fifteen minutes after injection of sumatriptan, the baseline pain scores decreased.25,26
- After oral treatment, the visual analog score for pain also decreased significantly, and this effect persisted after treatment discontinuation for a week. The main side effect like dizziness and rebound headaches are common for which there is lack of adherence to therapy.

Intranasal carbon dioxide (CO2):

- CO2 has always been considered a pain modulator in hyperactive neurons. Recent studies have shown that CO2 is a nociceptive modulator of afferent active trigeminal neurons based on the hypothesis that CO2 causes a decreased mucosal pH and that in turn activates the nociceptive effect of primary trigeminal afferent neurons.27
- A controlled, randomized, parallel-group study investigated the effects of intranasal CO2 on the transient receptor potential cation channel subfamily V member 1 (TRPV1)–mediated experimental trigeminal pain in healthy volunteers. Only mild modulatory effect of intranasal insufflation of CO2 at flow rates of 1 L/min was found, but the clinical utility seemed limited since changes in pain ratings were therapeutically irrelevant.28
- Hence, another phase 2 placebo-controlled trial was undertaken in which CO2 and placebo were administered in TN patients for 1 minute. All patients received three doses of CO2 and placebo each, and it was found that CO2 had improved effect on VAS scores. The trial is underway and its results are yet to be published (ClinicalTrials.gov identifier: NCT02473016).29

Calcium channel blockers (CCBs):

- Usually, in patients with continuous pain mediated by other pathophysiological mechanisms, a monotherapy with sodium channel blocker is not sufficient to control pain and other drugs are usually needed. CCBs and antidepressants have been advocated in the treatment of trigeminal neuralgia in patients not relieved by monotherapy with sodium channel blockers.30 Thus, apart from few case reports or cohort studies there is very little evidence on management of continuous pain and more studies with CCBs are warranted

Miscellaneous drugs:

- Various other medications like topical capsaicin, lignocaine, misoprostol, and intranasal lignocaine are available but their widespread use is not advocated at present.
- Misoprostol, a prostaglandin E1 analogue, showed efficacy in TN.
- Few studies reported the efficacy of misoprostol in a total of 27 patients with TN secondary to multiple sclerosis.31
- However, there is insufficient evidence to support or refute the use of this drug in TN.

Neural prolotherapy:

- Neural prolotherapy has been described in relation to the management of TN. It is also known as perineural injection therapy (PIT) and is one of the latest advancements in regenerative medicine. First described by Dr. Paul Pybus and Dr. Roger Wyburn-Mason, PIT targets neurogenic inflammation in subcutaneous nerves that potentially generates pain.43
- The technique involves injection of hypertonic dextrose saline with local anesthetics at the trigger points and usually requires multiple sittings.44

Nerve combing:

- Nerve combing, also called internal neurolysis, is a kind of surgical strategy that splits the branches of trigeminal nerve longitudinally using a special fiber knife based on preoperative pain locations and intraoperative finding.
- Jie et al studied 60 patients who achieved good pain relief following nerve combing.45
- Nerve combing has a much higher pain relief rate in patients without vascular compression than those with vascular compression.

Carbon dioxide laser:

- A CO2 laser is used to ablate the peripheral nerve in patients with drug refractory TN. Recently, it has been shown to reduce the pain scores in TN and persistence of pain relief till 12 months.42 The authors ablated peripheral nerves using low-power defocused mode; however, there was prolonged paresthesia of the affected nerves with this technique.

Low level laser therapy (LLLT):

- LLLT uses a single wavelength light source and works on the principle that irradiation with monochromatic light may affect cell function.40This technique involves irradiation of the region of interest followed by laser puncture at predetermined points along the course of the nerve. In a recent systematic review (8 randomized controlled trials, 2 prospective studies, and 3 case series) which evaluated the efficacy of LLLT for the therapeutic management of neuropathic orofacial pain, Pedro et al found a reduction in pain intensity in all studies (most of them significant).41 However, more quality studies assessing all outcome measures of chronic pain are warranted.

The Effect of Low-level Laser Therapy on Trigeminal Neuralgia: A Review of Literature

Farnaz Falaki, [1] Amir Hossein Nejat, [2] and Zohreh Dalirsani [3,*]

- Abstract

The effect of low intensity laser radiation in the treatment of acute and chronic pain is now established in many studies. Tri-geminal neuralgia is a pain passes through nerve's branches and its trigger is located in skin or mucosa that could lead to pain with a trigger stimulus. The pain involved branches of trigeminal nerve that sometimes has patients to seek the treatment for several years. Nowadays different treatments are used for relief of pain that most of them cause tolerance and various side effects. This paper reviews and summarizes scientific papers available in English literature publishedin PubMed, Scopus, Science Direct, Inter science, and Iran Medex from 1986 until July 2011 about the effect of these types of lasers on trigeminal neuralgia which is one of the most painful afflictions known. In different studies, the effect of laser therapy has been compared with placebo irradiation or medicinal and surgical treatment modalities. Low-level laser therapy (LLLT) is a treatment strategy which uses a single wavelength light source. Laser radiation and monochromatic light may alter cell and tissue function. However, in most studies laser therapy was associated with significant reduction in the intensity and frequency of pain compared with other treatment strategies, a few studies revealed that between laser and placebo group there was not any significant difference according to the analgesic effect. Low-level laser therapy could be considered in treatment of trigeminal neuralgia without any side effects.

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Low Level Laser Therapy for the treatment of Trigeminal Neuralgia after Oral surgeries: Two Different Applications

Intsar Waked; Asmaa Attalla; Marwa Eid.

- **Abstract**
  Background: Trigeminal neuralgia is an inflammation of the trigeminal nerve, causing intense facial pain.
  Objectives: The major purposes of this study were to evaluate the effect of laser therapy in Trigeminal neuralgia and to compare between different points of application.
  Materials and Methods: Forty five patients suffering from trigeminal neuralgia post oral surgery were selected after initial evaluation and diagnosis, patients were randomly divided into three groups of equal number. (E1); received LLLT through trigger point application and (E2); received LLLT through nerve path application while Control group (C) received placebo LLLT. The intensity of pain was measured by numerical rating scale.
  Results: The results of study showed that there were significant reduction of pain in experimental groups (E1& E2) with percentage of improvement 45% & 34% respectively more than control group (C).
  Conclusion: LILT was more effective than placebo in trigeminal neuralgia and the trigger points application was superior to nerve path application.

Neuromodulation:

- It is a new prospect in the management of TN patients, targeting either neural stimulation or inhibition to restore normal neurological function. Various neuromodulation techniques have been recently explored for the management of TN. These include transcranial magnetic stimulation, motor cortex stimulation, deep brain stimulation, spinal cord stimulation, transcutaneous electrical nerve stimulation, and peripheral nerve stimulation.
- A recent study is underway to establish the feasibility of using transcranial magnetic stimulation (TMS) for chronic orofacial pain in the interim period before surgery. Participants were randomized to either receive TMS or sham-TMS (a nontherapeutic TMS coil which sounds and feels similar to normal TMS), or standard treatment during the weeks of wait time before surgery. The sham TMS is a subtherapeutic level of magnetic stimulation which makes the same sound as normal TMS and causes a similar tingling of the skin.
- All study patients were asked to fill out an online survey about pain during different time points of the study. The complete results are not yet available, but preliminary results indicate that TMS, when applied to the head for a few minutes, has been shown to reduce pain in people with chronic orofacial pain of TN (ClinicalTrials.gov identifier: NCT04120129).37 Few studies have been conducted based on these techniques with variable success rate

Cryotherapy:

- To overcome the drawbacks of conventional cryotherapy such as incomplete pain relief and recurrence, few modifications have been suggested. These include (a) the use of a curved cryoprobe, (b) maintaining optimal temperature and pressure throughout the surgical procedure, (c) scoring of the epineurium, (d) application of petroleum jelly around the nerve before the introduction of the cryoprobe, and (e) delivery of three cycles of 3-minute freezing and 5-minute thawing to each nerve.35
- In a study, Bansal et al showed that a closed curved cryoprobe tip when used with nitrous oxide at a temperature of–98°C and a pressure of 70 kg/cm2 or 100 psi provided excellent analgesia. Almost 48.97% patients had pain-free interval of 36 to 40 months. The side effect was loss of fine and crude sensation over face for 6 to 24 months.36

Pulsed radiofrequency (PRF):

- PRF uses brief pulses of higher frequency alternate current to produce the same voltage or even higher fluctuations than during conventional radiofrequency (RF) treatment. PRF does not produce thermal lesions but there are microdamages within axonal microfilament and microtubules, especially in the pain-carrying C fibers.32
- Recent studies have shown that combination of both PRF and RF lesioning (RFL) has similar results in achieving a pain relief with lesser side effects than RFL alone.33
- There is also less number of complications like anesthesia dolorosa and hyperesthesia with PRF. To achieve better results, PRF and RFL should be used in tandem rather than using these modalities separately.

Ozone injection around gasserian ganglion (OIAGG):

- Some newer studies have explored the role of OIAGG. In a multicentric retrospective study, the authors injected an ozone–oxygen mixture gas at a concentration of 30 μg/mL into the area around the gasserian ganglion performed under C-arm X-ray guidance. The results showed that pain relief rates at posttreatment, 6 months, 1 year, and 2 years after the procedure were 88.35%, 86.87%, 84.46%, and 83.30%, respectively ($p < 0.05$).34
- A regression analysis found out that preoperative structural nerve damage was associated with less clinical effect or poor outcome. The study confirmed that OIAGG is a safe and effective modality for pain management in refractory TN.

Complimentary medicine:

- Apart from standard conventional therapy there are several complimentary therapies that aid in pain relief of TN. These include standard acupuncture, electroacupuncture, and spinal regulation therapies.14 Other modalities of complimentary medicine include sound therapy; low-intensity and low-frequency acoustic ultrasound patch; and vitamin B, C, and biofeedback.

The molecular medicine perspective emphasizes cellular and molecular phenomena and interventions rather than the previous conceptual and observational focus on patients and their organs.

The ACP (Autologous Conditioned Plasma) or PRP (Platelet Rich Plasma).

- Many serious illnesses or injuries of the human body are healing by themselves, e.g. without medical intervention. The concept behind this tendency of "natural self-healing" is an extreme complex biological system. Science is currently searching for answers to better understand this phenomenon.
- These therapies are effective for a large number of overuse injuries, injuries, and degenerative disease and for an accelerated healing following surgery. The ACP or PRP therapy does not have any side effects.
- From the combined experience of administering ACS to more than 100,000 human and 40,000 equine patients during a 15-year period it can be concluded that ACS is safe. Side effects are rare, the most common being a transient, local inflammatory response.

Abbrivation

ACS	Autologous conditioned serum
bFGF	Basic fibroblast growth factor (also FGF-2)
HGF	Hepatocyte growth factor
IGF-1	Insulin-like growth factor-1
IL-1β	Interleukin 1 beta
IL-1Ra	Interleukin 1 receptor antagonist
IL-7	Interleukin 7
NGF	Nerve growth factor
PDGF-AB	Platelet derived growth factor
TGF-β1	Transforming growth factor beta 1

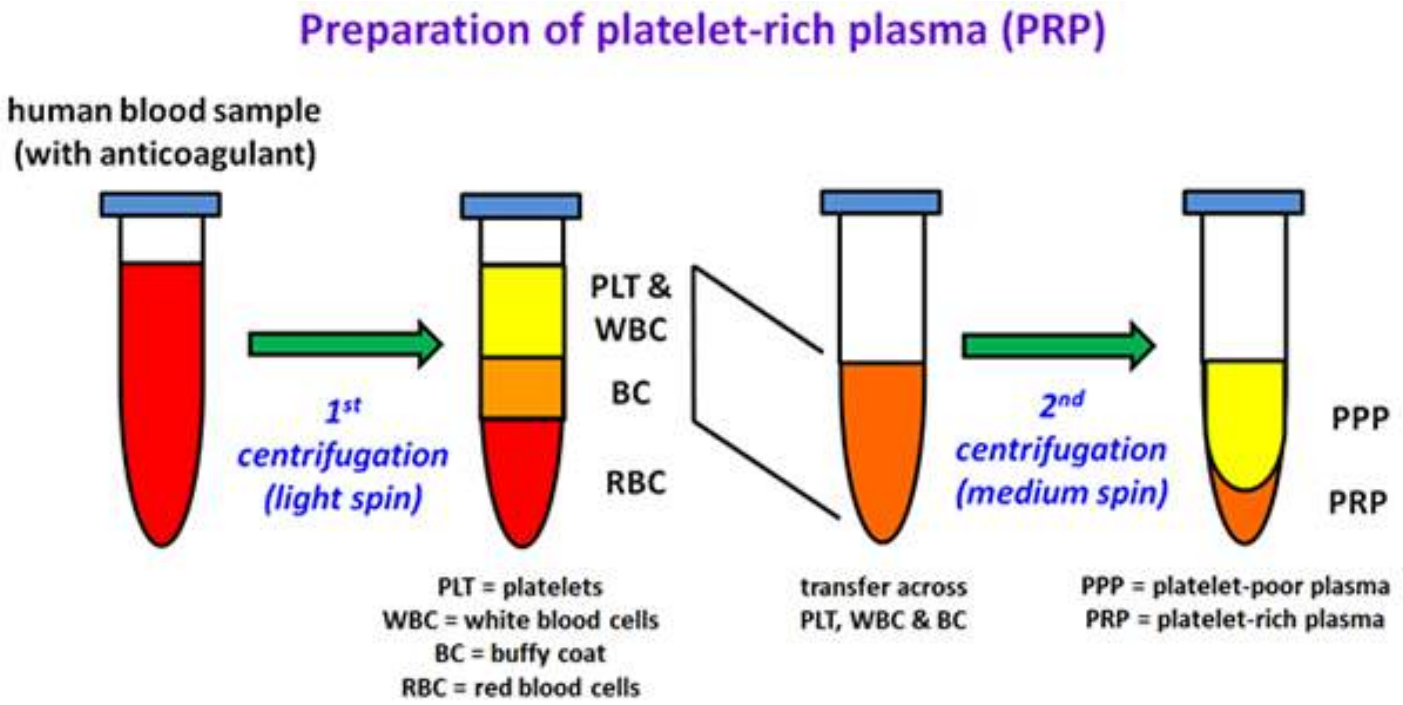
Autologous conditioned serum (ACS)

- Autologous conditioned serum (ACS) is an autologous blood product enriched in the interleukin-1 receptor antagonist (IL-1Ra), a naturally occurring inhibitor of interleukin- 1 (IL-1).
- ACS is administered locally to treat conditions in which IL-1 is thought to be an important agent of pathologic conditions. Several reviews have been written on this topic IL-1Ra has been produced in *Escherichia coli* as the recombinant molecule ana- kinra, marketed as Kineret.
- Anakinra, in combination with methotrexate, is approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis (RA), self-administered subcutaneously at a daily dose of 100 mg.
- However, sys temic anakinra is effective in systemic juvenile idiopathic arthritis and a variety of rare autoinflammatory disorders; it is also of benefit in gout and pseudogout.

- Anti-inflammatory cytokines are also present in abundance in the synovial membrane, synovial fluid and cartilage in patients with OA. Examples include IL-4, IL-10 and IL-13. Important properties of these cytokines are the reduction of IL-1b, TNF-a and MMPs, and the increased production of IL-1Ra [27].
- IL-1Ra was first reported in 1985 and was discovered in human macro- phages cultured on IgG and eventually in macrophages in the synovium in OA [24]. The human *IL-1Ra* gene was mapped to band q14-q21 in the long arm of chromosome 2.
- Three structural variants have been identified: a 17-kDa form secreted from mono- cytes (sIL-1Ra); an 18-kDa form that remains in the cytoplasm of keratinocytes (icIL-1Ra); and a 16-kDa form discovered intra-cellularly in neutrophils, monocytes and hepatocytes [36].
- Later, the IL-1Ra genome was cloned and expressed in *Escherichia coli* producing the 18-kDa molecule. An identical IL-1Ra protein was made by stimulation of human monocytes with granulocyte colony-stimulating factor [35,37,38].
- As the factors responsible for the development of OA become well understood, therapeutic agents targeting aspects of the pathophysiological pathways have attracted particular interest. Such areas of interest include the inhibition of cytokines, particularly IL-1b, which seems to be the principal cytokine responsible for the inflammatory changes found in OA, and the MMPs, which play a role in the degradation of the cartilage matrix.

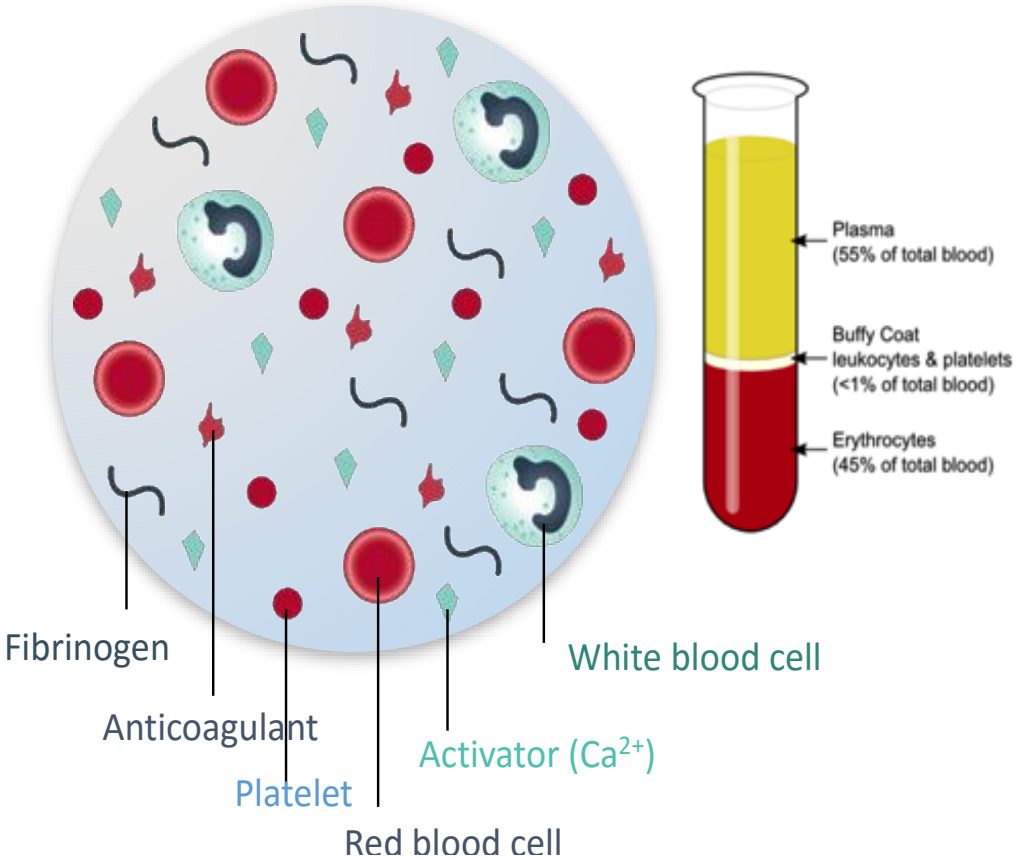
PRP preparation

- Leukocyte
- Count



PRP	ACP	ACS®

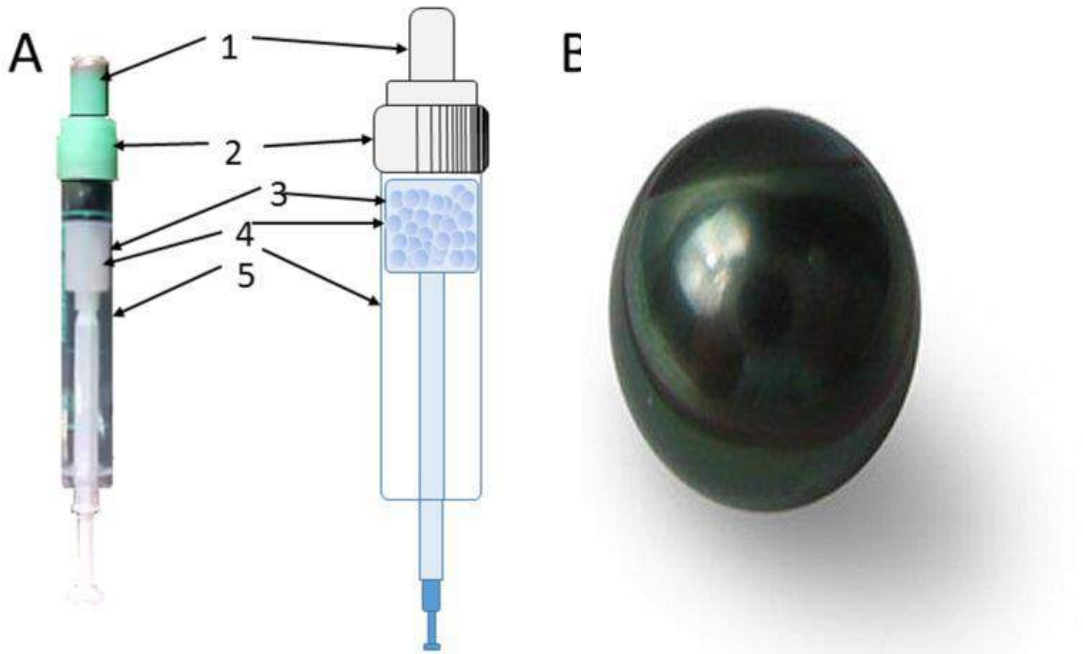
- Plasma contains cells, clotting factors and additives
- Serum is cell-free and clotting factor free, and contains no additives

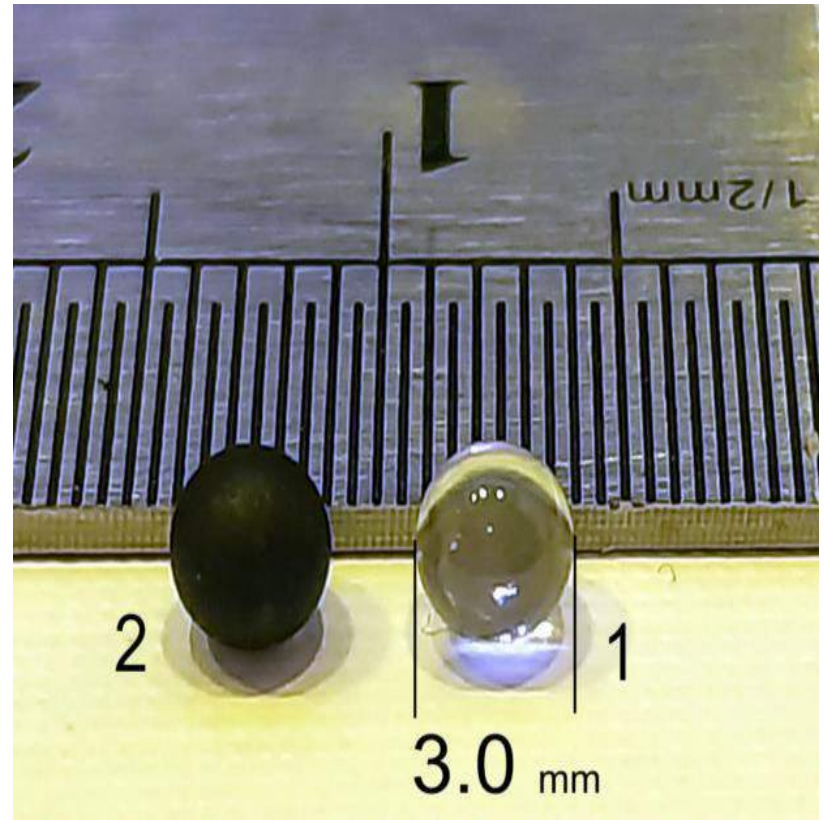


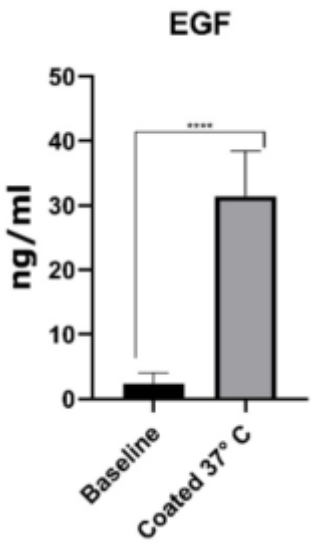
No platelets –
No white blood cells –
No red blood cells –
No additives –

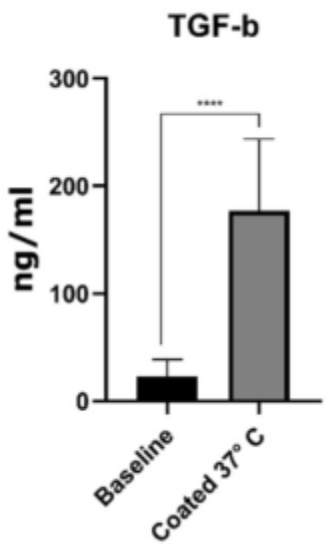
Table 1
Cytokines and growth factors present in autologous conditioned serum

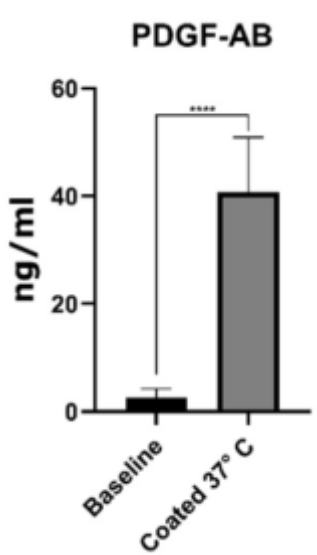
Cytokine	N	Basal Concentration	Concentration in ACS
IL-1Ra	224	236	2015
IL-1β	224	UD	7.9
IL-6	200	UD	28.7
TNF-α	92	UD	10.1
IL-10	92	UD	33.4
FGF-2	92	14.6	26.6
VEGF	92	61	508.6
HGF	92	431	1339
IGF-1	92	86,000	117,209
PDGF AB	92	205	39,026
TGF-β	80	1165	97,939

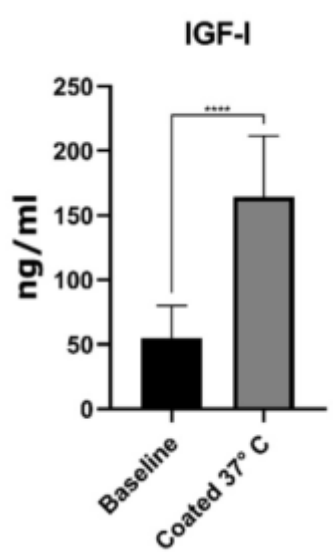

A
1
2
3
4
5
B

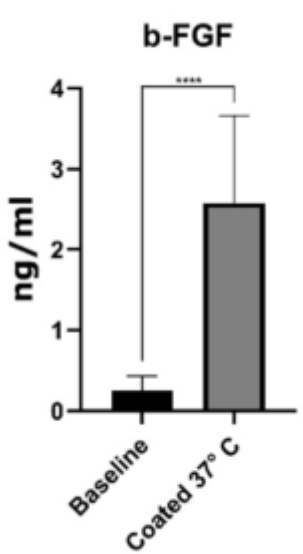

2
1
3.0 mm


EGF
ng/ml
50
40
30
20
10
0
****
Baseline
Coated 37° C

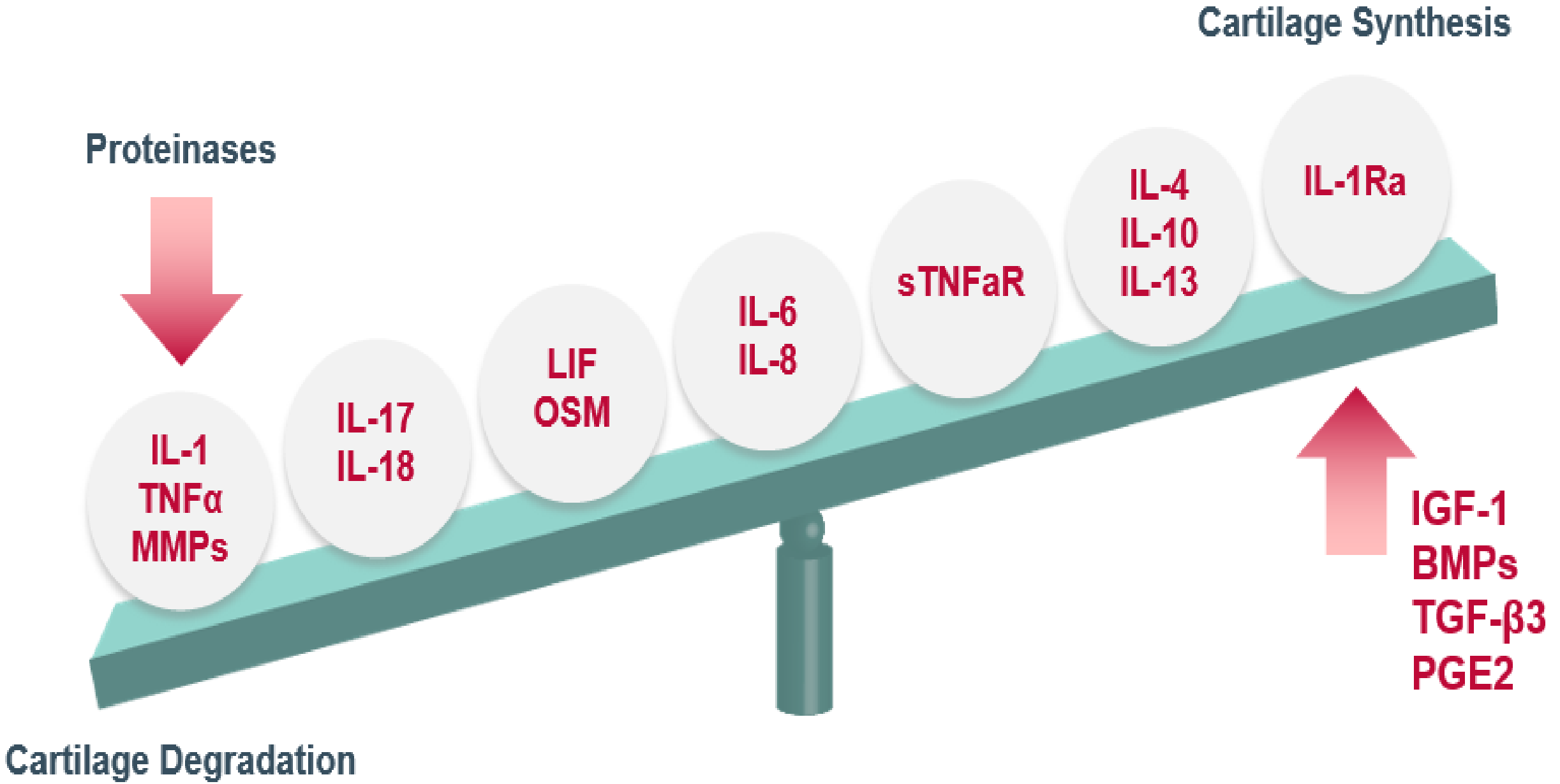

TGF-b
ng/ml
300
200
100
0
****
Baseline
Coated 37° C


PDGF-AB
ng/ml
60
40
20
0
****
Baseline
Coated 37° C


IGF-I
ng/ml
250
200
150
100
50
0
****
Baseline
Coated 37° C


b-FGF
ng/ml
4
3
2
1
0
****
Baseline
Coated 37° C

	Baseline		Coated	
	Mean	SD	Mean	SD
IL1bRa	345/9	146/3	12953	4090
IL1b	<3.9	<3.9	61/19	43/06
IL4	2/83	1/17	12/3	5/47
IL6	10/28	4/786	59/76	19/14
IL8	9/690	4/122	34/16	10/80
IL10	8/14	4/77	32/14	9/948
IL13	67/99	18/89	95/47	23/33
EGF	2/38	1/63	31/44	7/007
TGFb	22/88	15/69	177/1	66/54
bFGF	0/254	0/176	2/577	1/085
IGF	54/82	25/28	164/5	47/09
PDGFAB	2/57	1/71	40/71	10/20


Cartilage Synthesis
Proteinases
IL-1
TNFα
MMPs
IL-17
IL-18
LIF
OSM
IL-6
IL-8
sTNFaR
IL-4
IL-10
IL-13
IL-1Ra
IGF-1
BMPs
TGF-β3
PGE2
Cartilage Degradation

Therapeutic Advances in
Musculoskeletal Disease

Unofficial 2015 Impact Factor: 4.190, based on data from Thomson Reuters Web of Knowledge | Indexed in PubMed/PubMedCentral | Indexed in Emerging Sources Citation Index (ESCI): a new index in the Web of Science (TM) Core Collection

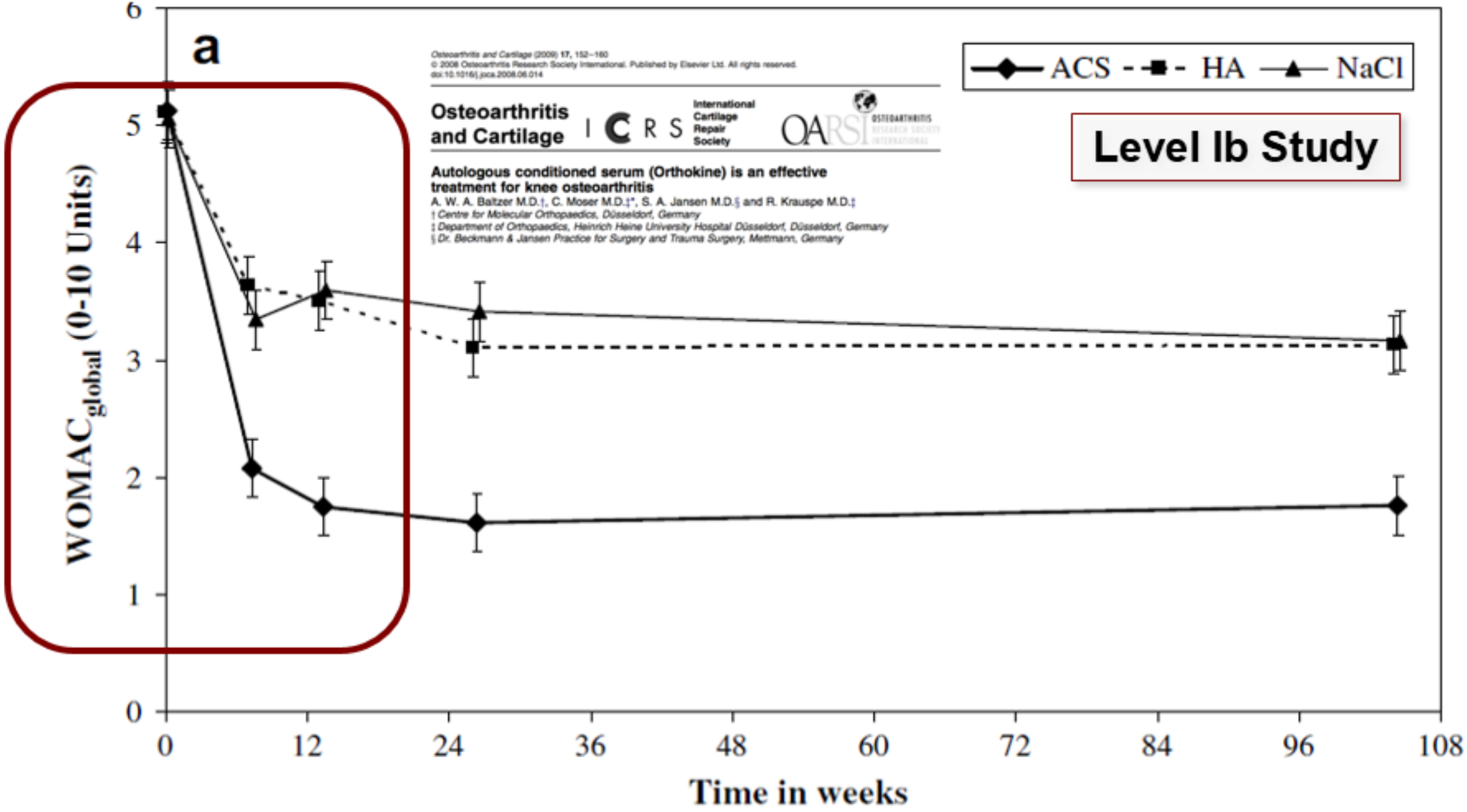
How does surgery compare with advanced intra-articular therapies in knee osteoarthritis: current thoughts

This Article

Published online before print April 18, 2016, doi: 10.1177/1759720X16642405

Intra-articular injection of ACS (Orthokine) has demonstrated **efficacy as a treatment for knee OA** in a number of studies, with a very low rate of adverse events and side effects, compared with surgery. Treatment with ACS utilizes the release of anti-inflammatory cytokines and regenerative growth factors to support the natural healing processes in the knee...

Per-protocol population N = 188



Osteoarthritis and Cartilage (2009) 17, 152–160

doi:10.1016/j.joca.2008.06.014

Osteoarthritis and Cartilage

International Cartilage Repair Society

Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis

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§ Dr. Beckmann & Jansen Practice for Surgery and Trauma Surgery, Mettmann, Germany

Level Ib Study

PLOS ONE

RESEARCH ARTICLE

Treatment of Osteoarthritis of the Knee with a Combination of Autologous Conditioned Serum and Physiotherapy: A Two-Year Observational Study

Jaime Baselga García-Escudero*, Pedro Miguel Hernández Trillos

Hospital Ruber International, Madrid, Spain

Level IIa Study

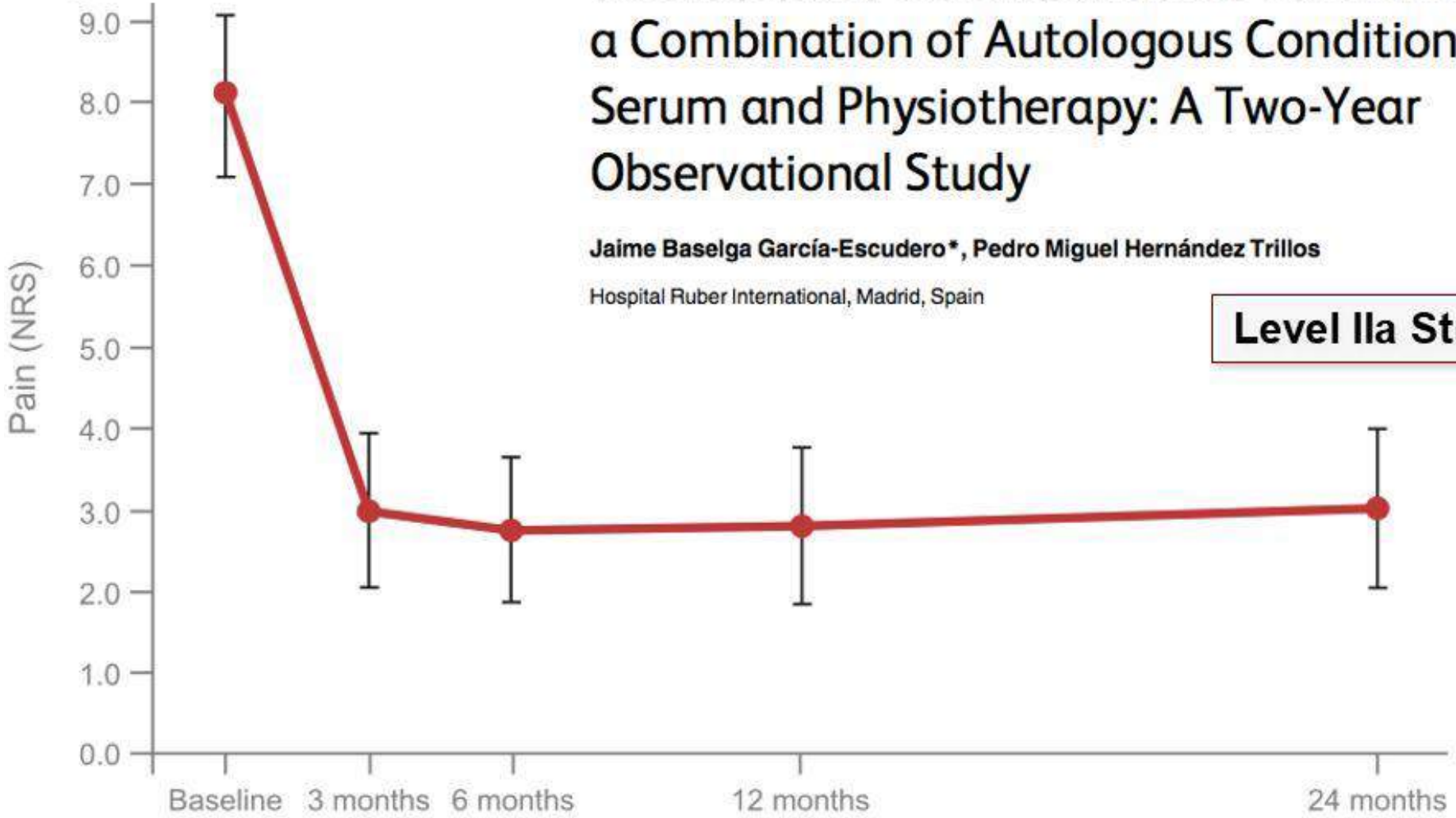


Fig 1. Pain (NRS) scores for baseline, 3, 6, 12 and 24 months after treatment with ACS and physiotherapy. Error bars denote standard deviation. ACS: Autologous conditioned serum; NRS: Numeric Rating Scale.

Efficacy of Epidural Perineural Injections With Autologous Conditioned Serum for Lumbar Radicular Compression

An Investigator-Initiated, Prospective, Double-Blind, Reference-Controlled Study

Level Ib Study

Cordelia Becker, MD,* Stefan Heidersdorf, MD,† Sascha Drewlo, MSc,‡
Sonja Zirke de Rodriguez,† Juergen Krämer, MD,† and Roland Ernst Willburger, MD§

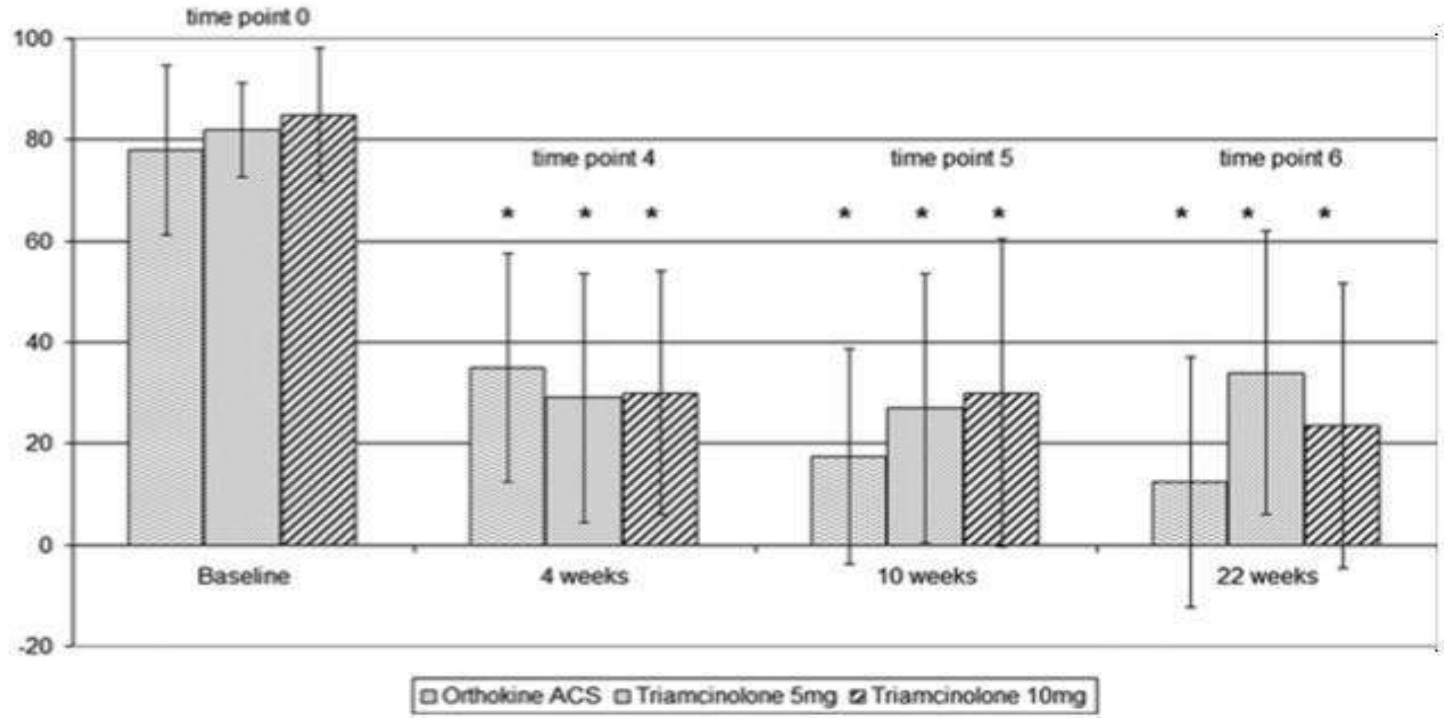
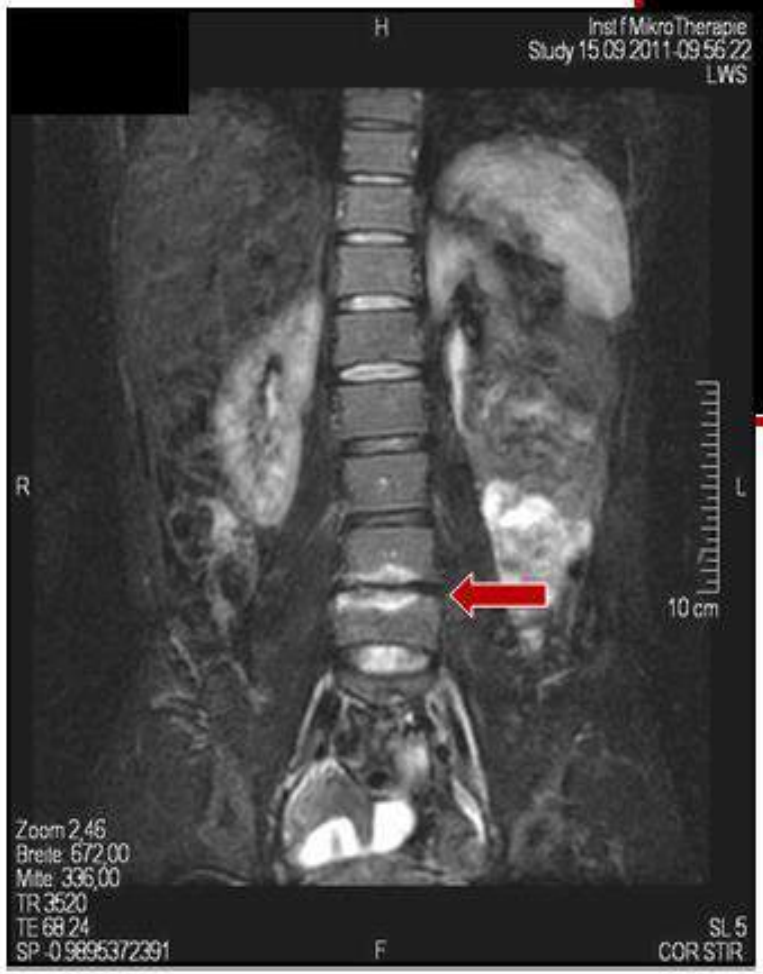
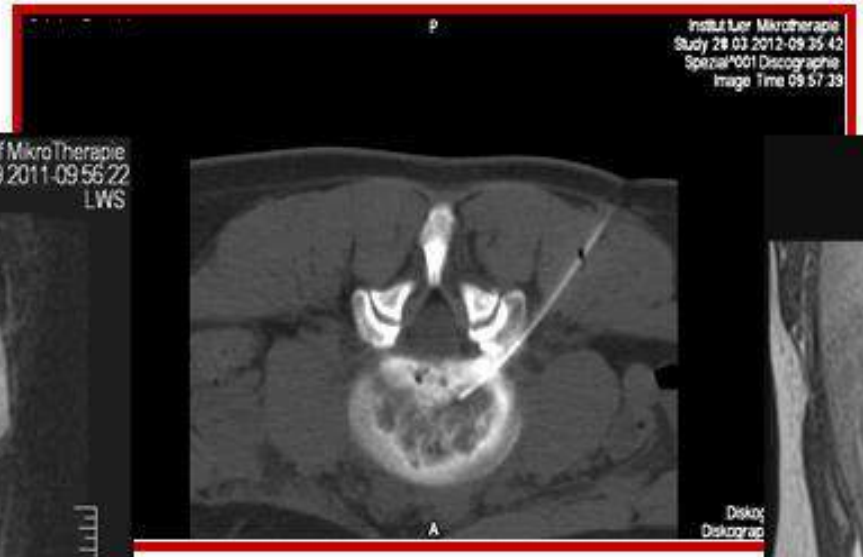


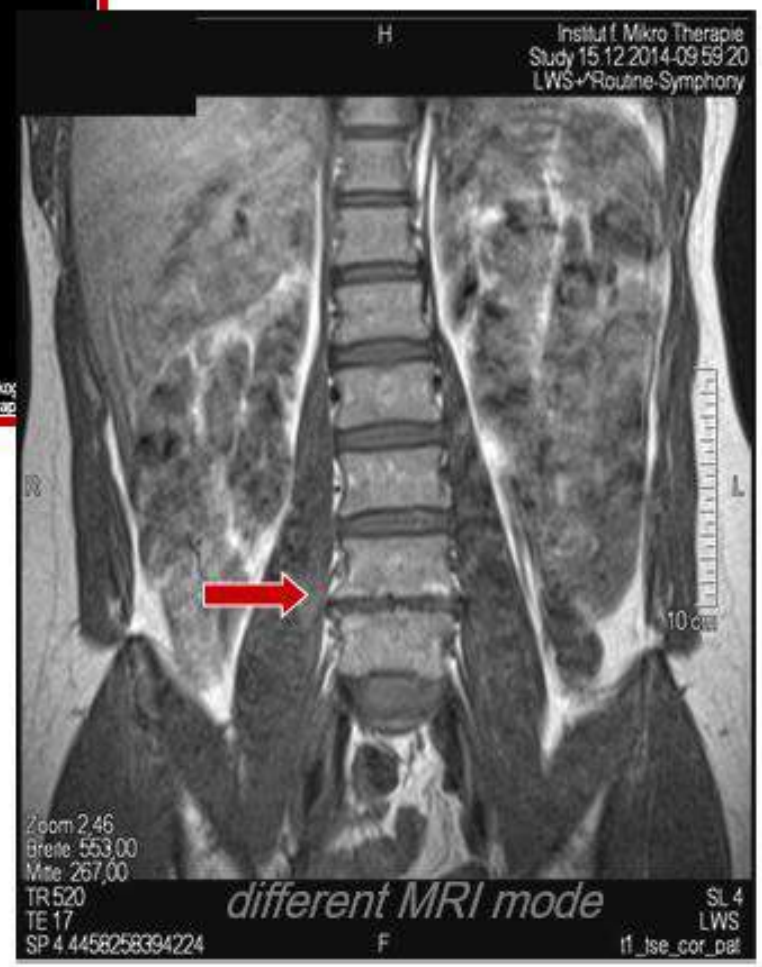
Figure 1. Results for the primary study endpoint. The pain intensity scores and the time curves for VAS are shown. Mean, SD, and median are given. *Significant difference from baseline. Time schedule is given in weeks after the first injection.



before



3 intradiscal injections



after

30 mths later (painfree)

Courtesy of Grönemeyer Institute, Bochum

Growth factors and cytokines in wound healing

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Email: tomicm@hss.edu

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ABSTRACT

Wound healing is an evolutionarily conserved, complex, multicellular process that, in skin, aims at barrier restoration. This process involves the coordinated efforts of several cell types including keratinocytes, fibroblasts, endothelial cells, macrophages, and platelets. The migration, infiltration, proliferation, and differentiation of these cells will culminate in an inflammatory response, the formation of new tissue and ultimately wound closure. This complex process is executed and regulated by an equally complex signaling network involving numerous growth factors, cytokines and chemokines. Of particular importance is the epidermal growth factor (EGF) family, transforming growth factor beta (TGF-β) family, fibroblast growth factor (FGF) family, vascular endothelial growth factor (VEGF), granulocyte macrophage colony stimulating factor (GM-CSF), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), interleukin (IL) family, and tumor nerosis factor-α family. Currently, patients are treated by three growth factors: PDGF-BB, bFGF, and GM-CSF. Only PDGF-BB has successfully completed randomized clinical trials in the Unites States. With gene therapy now in clinical trial and the discovery of biodegradable polymers, fibrin mesh, and human collagen serving as potential delivery systems other growth factors may soon be available to patients. This review will focus on the specific roles of these growth factors and cytokines during the wound healing process.

Treatment of Muscle Injuries by Local Administration of Autologous Conditioned Serum: A Pilot Study on Sportsmen with Muscle Strains

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P. Klein[2]
P. Schäferhoff[2]
H. J. Appell[3]
L. M. Mir[1]
P. Wehling[4]

Level Ib Study

Table 2 Recovery time after moderate muscle strains in professional sportsmen

Strained muscle	*Recovery time (days) in autologous conditioned serum group*	*Recovery time (days) in control Actovegin®/ Traumeel® group*
Hamstring	12, 14, 16, 17, 18, 21	16, 18, 23, 24, 28
Adductor	10, 15, 17, 18, 21, 23	19, 24, 25, 26
Iliopsoas	17, 21	24
Gluteus	20	
Abdominal oblique	8	
Gastrocnemius	14	18
Rectus femoris	16	
Mean	16.6	22.3
SE	0.9	1.2

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Wound Repair Regen. 2014 ; 22(5): 569–578. doi:10.1111/wrr.12205.

Clinical Application of Growth Factors and Cytokines in Wound Healing

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Abstract

Wound healing is a complex and dynamic biological process that involves the coordinated efforts of multiple cell types and is executed and regulated by numerous growth factors and cytokines. There has been a drive in the past two decades to study the therapeutic effects of various growth factors in the clinical management of non-healing wounds (e.g. pressure ulcers, chronic venous ulcers, diabetic foot ulcers). For this review, we conducted a nonline search of Medline and Pub Medical and critically analyzed the literature regarding the role of growth factors and cytokines in the management of these wounds. We focused on currently approved therapies, emerging therapies and future research possibilities. In this review we discuss four growth factors and cytokines currently being used on and off label for the healing of wounds. These include: granulocyte-macrophage colony stimulating factor (GM-CSF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF). While the clinical results of using growth factors and cytokines are encouraging, many studies involved a small sample size and are disparate in measured endpoints. Therefore, further research

ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
June 2020; 19(3):243-252.
Doi:

Effect of Dextrose Prolotherapy, Platelet Rich Plasma and Autologous Conditioned Serum on Knee Osteoarthritis: A Randomized Clinical Trial

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[2] Stem Cell Research Center, Tabriz University of Medical Science, Tabriz, Iran
[3] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[4] Stud Road Medical Centre, Dandenong, VIC, Australia
[5] Department of Medical Laboratory Sciences, Faculty of Allied Medicine, Gonabad University of Medical Sciences, Gonabad, Iran
[6] Medical Biotechnology Research Center, AJA University of Medical Sciences, Tehran, Iran
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ABSTRACT

Knee osteoarthritis (OA) is one of the common degenerative articular disorders that are related to decreased quality of life. Currently, novel biologic therapeutic approaches are introduced in the literature for OA management. In this study, the clinical efficiency of Dextrose prolotherapy, platelet-rich plasma (PRP) and autologous conditioned serum (ACS) injection on the level of pain and function in Knee OA were compared.

A randomized clinical trial was directed on 92 knee OA patients. Patients were randomly divided into three groups: 30 were received dextrose prolotherapy once in a week for three weeks, 30 received autologous PRP for two times with seven days interval, and in the remaining 32 patients 2ml of ACS were injected two times every seven days. Study participants were measured through the Western Ontario and McMaster Universities (WOMAC) score, the visual analogue scale (VAS), at baseline, 1 and 6 months post-intervention.

Both ACS and PRP treated patients showed improvement in pain intensity and knee function during 1 and 6 months pursue; however, this progress was more significant in the ACS group. Dextrose prolotherapy showed no substantial changes in pain and function of the affected knee in treated patients.

Treatment of Knee OA with ACS and PRP injections are associated with pain reduction and knee function improvement. Not only, ACS therapy is more effective than that of PRP, but also due to its less variability in processing and less reported side effects, it could be considered as a safe and effective non-surgical alternative for OA management.

Platelet-rich Plasma Preparation

For PRP preparation, about 20 mL of venous blood was drained under aseptic precautions each time. Then, centrifuged two times, first at 1600 rpm for 13 minutes to separate erythrocytes, and a second at 3500 rpm for seven minutes to concentrate platelets to yield a PRP unit. The unit of PRP was contained 4X concentration of platelets and the lowest leukocyte. Platelet concentrate was injected into the knee joint by a skilled specialist under aseptic conditions two times every seven days through the supra-lateral approach. The knees were immobilized for 10 minutes after injection.

Autologous Conditioned Serum (ACS) Preparation

20 mL of whole blood was taken from each patient under aseptic condition by sterile syringes containing glass beads. A combination of bioactive materials coated the glass beads, binder resin and additives to secure adhesion of the materials to the glass beads. Blood filled syringes incubated for 6-9 hours in 37oC to induce the production of IL-1Ra by white blood cells in whole blood. The blood-filled syringes were centrifuged after incubation, and the serum supernatant was separated. After aseptic harvesting, the serum was used. Autologous conditioned serum (2 mL) was injected into the knee joint by a skilled specialist under aseptic conditions two times every seven days through the supra-lateral approach.

Dextrose Prolotherapy Method

Dextrose prolotherapy solutions for maximum safety usually consist of sterile water, dextrose, and a small concentration of lidocaine. In this study, we used a combination of 50% dextrose (2 mL), bacteriostatic water (2 mL), and 2% lidocaine (1 mL). The small dose of lidocaine was used aimed at post-injection relief. Dextrose prolotherapy solutions were injected into the knee joint by a skilled specialist once a week for three weeks under the ultrasound guidance through the supra-lateral approach.

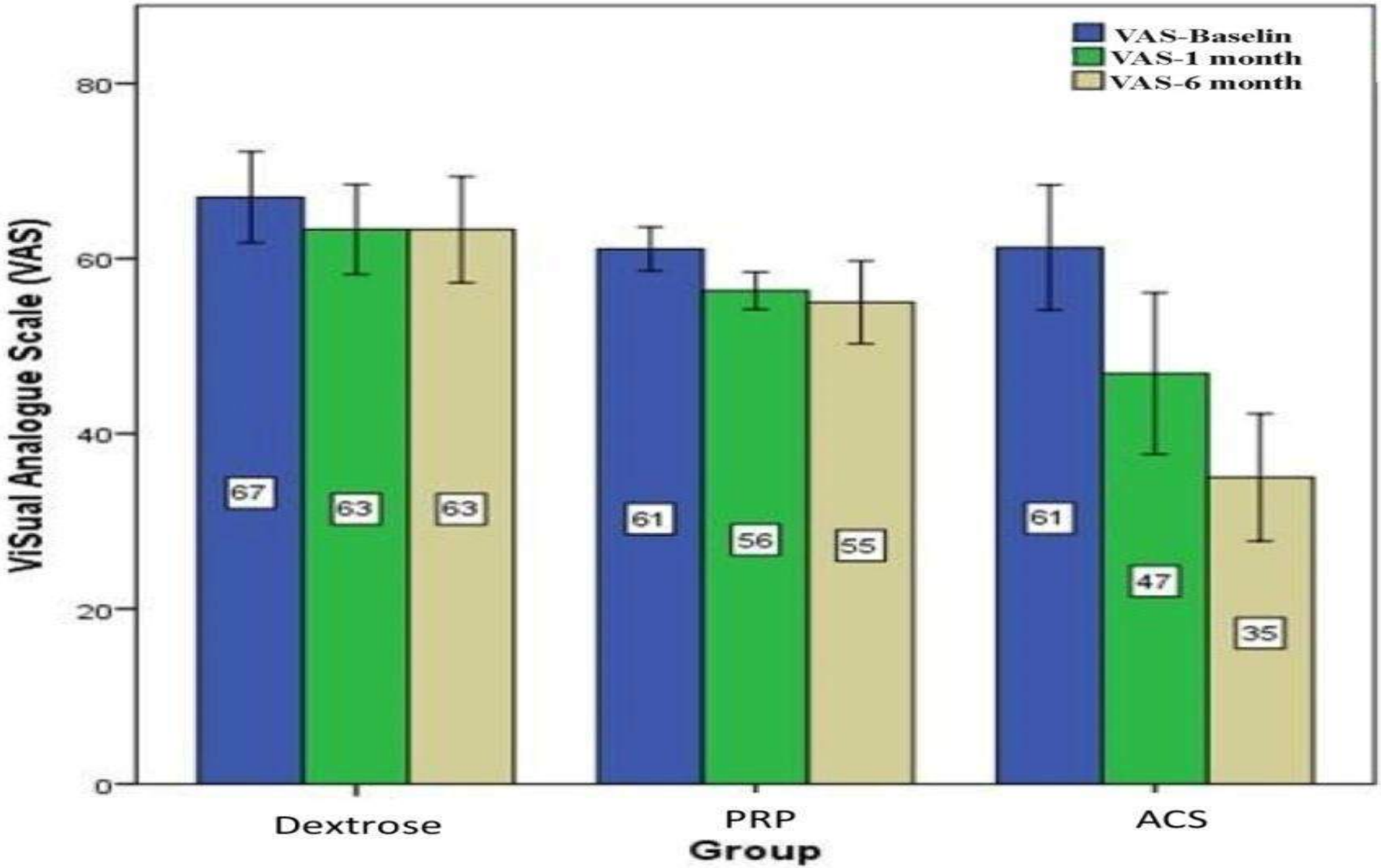
VAS-Baselin
VAS-1 month
VAS-6 month
ViSual Analogue Scale (VAS)
80
60
40
20
0
67
63
63
61
56
55
61
47
35
Dextrose
PRP
ACS
Group

Table 4
Effect sizes of various intra-articular treatments for osteoarthritis

	Effect Size	
Treatment	**Pain**	**Function**
Corticosteroids (1–4 wk)	<0.50	0.06
HA (24 wk)	<0.46	0.33
PRP (24–52 wk)	<0.40	0.40
ACS (24–104 wk)	<0.73	0.54

Effect sizes were calculated from RCT data published before January 2016.

Effect sizes range from 0 to 1 and can be considered as follows: less than 0.1, no effect; 0.1–0.29, small effect; 0.3–0.49, moderate effect; greater than 0.5, large effect.

The Potential of Topical and Injectable Growth Factors and Cytokines for Skin Rejuvenation

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Facial Plast Surg 2014;30:157–171.

Abstract

Growth factors and cytokines (referred to collectively hereafter as GFs) control cell growth, proliferation, and differentiation via a network of inter and intracellular signaling pathways. There are striking parallels between the pathways involved in skin wound healing and those implicated in photoaging of the skin. In recent years, topical and injectable GFs have emerged as an intriguing therapeutic modality that can be harnessed for aesthetic and medical purposes. This article provides a review of available evidence for the role in skin regeneration of topical GFs, and of injectable GFs contained in autologous platelet-rich plasma (PRP). It presents data from recent studies of GFs, offers a discussion of their potential to serve as antiaging actives, and includes safety considerations. As studies of injectable GFs typically assume preexisting familiarity with PRP protocols and the theory behind them, explanatory notes are provided. An assessment is provided of the evidence gaps that exist currently between experimental observations regarding GFs and their proven clinical benefits. Data of evidence levels II

Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Skin rejuvenation using cosmetic products containing growth factors, cytokines, and matrikines: a review of the literature

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Number of times this article has been viewed

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Abstract: Skin aging is primarily due to alterations in the dermal extracellular matrix, especially a decrease in collagen I content, fragmentation of collagen fibrils, and accumulation of amorphous elastin material, also known as elastosis. Growth factors and cytokines are included in several cosmetic products intended for skin rejuvenation because of their ability to promote collagen synthesis. Matrikines and matrikine-like peptides offer the advantage of growth factor-like activities but better skin penetration due to their much smaller molecular size. In this review, we summarize the commercially available products containing growth factors, cytokines, and matrikines for which there is evidence that they promote skin rejuvenation.

Keywords: cosmetics, skin, aging, growth factor, cytokine, matrikine

Skin anti-aging strategies

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[†]These authors contributed equally to this work.

Keywords: aging, anti-aging, antioxidants, laser, peeling, fillers, botulinum toxin, hormone replacement therapy, cell regulators, prevention

Skin aging is a complex biological process influenced by a combination of endogenous or intrinsic and exogenous or extrinsic factors. Because of the fact that skin health and beauty is considered one of the principal factors representing overall "well-being" and the perception of "health" in humans, several anti-aging strategies have been developed during the last years. It is the intention of this article to review the most important anti-aging strategies that dermatologists have nowadays in hand, including including preventive measurements, cosmetological strategies, topical and systemic therapeutic agents, and invasive procedures.

will yield improvement in skin appearance and will speed wound healing.[21] A marked loss of fibrillin-positive structures[22] as well as a reduced content of collagen type VII (Col-7), may contribute to wrinkles by weakening the bond between dermis and epidermis of extrinsically age skin.[23] Sun-exposed aged skin is characterized by the solar elastosis. The sparse distribution and decrease in collagen content in photoaged skin can be due to increased collagen degradation by various matrix metalloproteinases, serine, and other proteases irrespective of the same collagen production.[24-28] In older skin, collagen looks irregular and disorganized, the ratio of Col-3, to Col-1 has been shown to increase, due, significantly, to a loss of Col-1.[29] The overall collagen content per

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An autologous anti-aging serum confirms its beauty enhancer effect but its role as a chronic inflammation modulator is not clear

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Abstract: There are many biological theories that claim to be the final explanation of aging, though actually it is well accepted that none of them provides an explanation that allows a full understanding of the complicated, multi-factorial, unavoidable and deleterious aging process. Inflammation can be considered a core process of aging and vice versa, aging is sometimes referred as a chronic inflammatory state condition. AAS is highly concentrated in some growth factors and anti-inflammatory cytokines like Interleukin-1 receptor antagonist (IL-1ra). Evidence suggested that AAS had two very well differentiated clinical effects: a systemic "anti-inflammatory-anti-aging" action and a local aesthetic action. To confirm the two effects with a multisession protocol and to assess a possible correlation between them were the aims of this work.

Keywords: Aging, Autologous Antiaging Serum (AAS), Beauty, Interleukin-6, C Reactive Protein, Chronic Inflammation

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RESEARCH ARTICLE

Effects of Autologous Platelet-Rich Plasma on Endometrium Thickness and Pregnancy Rates During Intrauterine Insemination

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Abstract

Objective: Evaluation of the effect of platelet-rich plasma (PRP) on the endometrium and pregnancy outcomes in patients undergoing insemination due to unexplained infertility.

Methods: 24 patients who were admitted to the clinic due to unexplained infertility, analyzed retrospectively between March 2018 and October 2018. Gonadotropin induction was initiated on day 3 of the cycle for follicular growth. Human chorionic gonadotropin (hCG) was applied for ovulation induction at the point that at least 1 follicle that is over 16 mm was detected by transvaginal ultrasound. 17.5 ml of blood from the patient's venous system was drawn for the preparation of the PRP which includes 4-5 times more platelets than regular blood. PRP was administered to 12 patients (Group 1) on the hCG day, while hCG was solely administered to the other group (Group 2) and both groups were inseminated 36 hours later.

Results: The demographic properties of all patients were determined as follows: mean age; 29.13 years old (±3.4), mean infertility period; 1.96 years (±1.08), mean ovulation induction period; 7.92 days (±1.76), mean antral follicle count; 14.54 (±6.56), mean dominant follicle count; 2.04 (±0.75). Although there was no significant difference between the groups in terms of clinical pregnancy (3/12 vs 2/12, p: 0.623), the change in endometrial thickness was significantly higher in the PRP administered group (1.95 mm vs 0.44 mm, p< 0.001).

Conclusion: PRP application before the insemination seems promising for the preparation of the endometrium in patients having an inadequate endometrial thickness or in patients experiencing recurrent implantation failure.

Key words: Intrauterine insemination, endometrial thickness, autologous platelet-rich plasma, infertility, pregnancy rate

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Review article

Intrauterine infusion of autologous platelet-rich plasma in women undergoing assisted reproduction: A systematic review and meta-analysis

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ABSTRACT

Prior studies have provided conflicting results regarding the use of platelet-rich plasma (PRP) in women undergoing in-vitro fertilization (IVF) or intracytoplasmic injection (ICSI). The objective of this study was to evaluate the effect of the intrauterine infusion of PRP on the outcome of embryo transfer (ET) in women undergoing IVF/ICSI. We searched databases, including PubMed, Embase, Scopus, Web of Science, and the Cochrane Database of Clinical Trials (CENTRAL). Meta-analysis using a random-effects model was performed to calculate the pooled estimates. Seven studies involving 625 patients (311 cases and 314 controls) were included. The probability of chemical pregnancy (n − 3, risk ratio (RR): 1.79, 95 % confidence intervals (CI): 1.29, 2.50; $P < 0.001$, $I^2 = 0$ %), clinical pregnancy (n − 7, RR: 1.79, 95 % CI: 1.37, 2.32; $P < 0.001$, $I^2 = 16$ %), and implantation rate (n = 3, RR: 1.97, 95 % CI: 1.40, 2.79; $P < 0.001$, $I^2 = 0$ %) was significantly higher in women who received PRP compared with control. There was no difference between women who received PRP compared with control group regarding miscarriage (RR: 0.72, 95 % CI: 0.27, 1.93; P − 0.51, $I^2 - 0$ %). Following the intervention, endometrial thickness increased in women who received PRP compared to control group (SMD: 1.79, 95 % CI: 1.13, 2.44; $P < 0.001$, $I^2 = 64$ %). The findings of this systematic review suggest that PRP is an alternative treatment strategy in patients with thin endometrium and recurrent implantation failure (RIF). Further prospective, large, and high quality randomized controlled trials (RCTs) are needed to identify the subpopulation that would most benefit from PRP.

Original Article

Autologous Conditioned Serum (Orthokine) Injection for the Treatment of classical Trigeminal Neuralgia: Results of a Non-blinded One-arm Prospective Pilot Study

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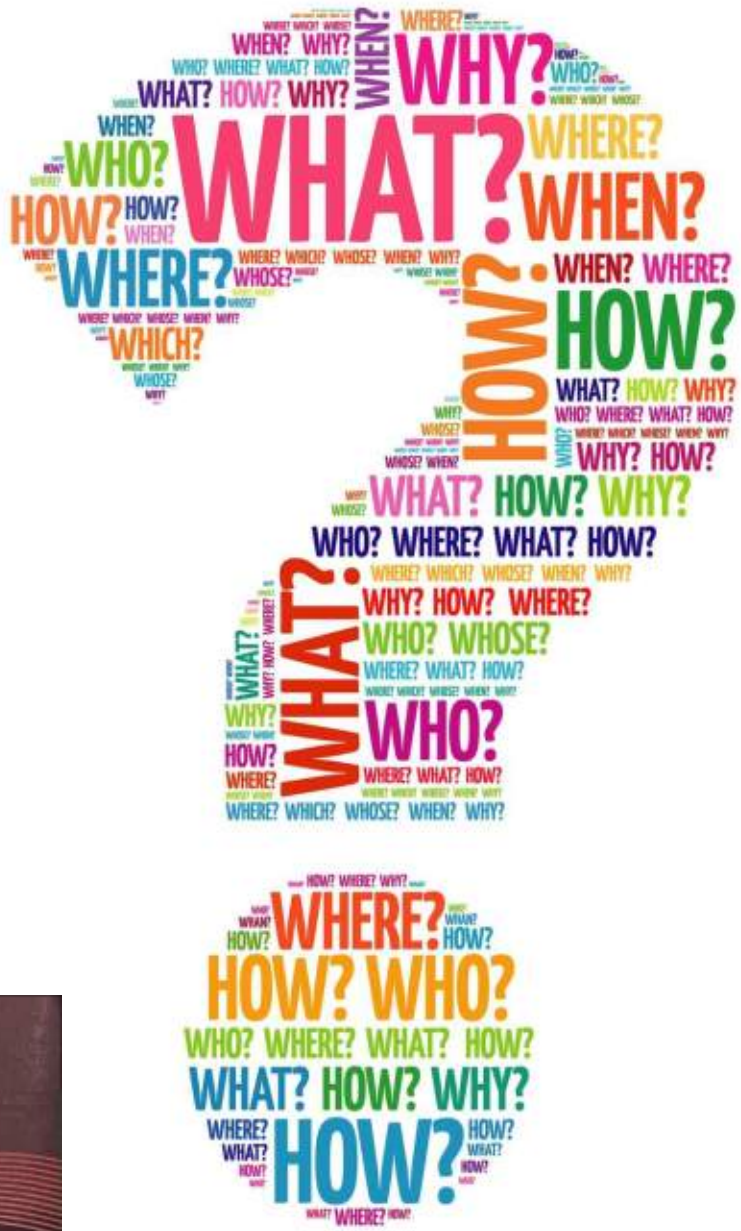
- **Abstract**
- **Background and Objectives:** In spite of existing advancements, trigeminal neuralgia (TGN) treatment remains a great challenge. We aimed to determine the efficacy and safety of autologous conditioned serum (Orthokine) injection into the foramen oval for the treatment of refractory TGN.
- **Materials and Methods:** We did a one-arm non-blinded pilot trial in Tabriz/Iran in the Pain & Palliative Care Department of Imam Reza University Hospital, Tabriz, Iran. Eleven qualified patients aged 18–80 years with established classical TGN were injected Orthokine (2 ml per injection) once per week for three consecutive weeks (totally four injections). Numeric Rating Scale scores for facial pain intensity and also carbamazepine daily dosage, at pretreatment (T0) and on week 1 (T1), week 2 (T2), week 3 (T3), week 4 (T4), and month two (T5) post-treatment were verified.
- **Results**: Pain intensity was significantly reduced in the first 3 weeks follow up period in comparison with the baseline (T0 to T3) (8.18±1.99 to 2.82± 2.13, p<0.001) which remains at week 4 (T4) and month 2 (T5) patient follow ups (2.82± 2.13 to 3.36± 2.69, p=0.886). Carbamazepine consumption was significantly reduced in the first 3 weeks follow up period in comparison to the baseline (T0 to T3) (636.36±307.48 to 200.00± 296.64, p=0.003) which remains at week 4 and month 2 follow ups (200.00± 296.64 to 200.00± 282.84, p=0.802). No serious adverse events were reported in participants.
- **Conclusion**: Our findings showed that Orthokine/Prothokine injection led to consistent pain relief and reduced Carbamazepine dosage in patients with TGN with acceptable safety.

Questions…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