Introduction to
New Treatment for Severe Pain of Herpes zoster Infections 211203

Subcutaneous TELTAB (**T**umescent **E**pinephrine **L**idocaine **T**riamcinolone **A**cyclovir **B_{12}** vitamin)

Herpes zoster Ophthalmicus (HZO)
Herpes zoster Oticus & Ramsay Hunt Syndrome (RHS)
Herpes zoster Mandibularis
Herpes Simplex Ophthalmicus (HSO)
Acute Herpes zoster (AHZ) & Postherpetic Neuralgia (PHN)

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Herpes zoster (HZ), commonly known as **shingles**, is a painful acute infection caused by the reactivation of the dormant Herpes zoster virus, in an individual who has previously had chicken pox, which is caused by the varicella zoster virus (VZV). Shingles can be extremely painful. New onset Acute Herpes zoster (AHZ) can be extremely painful even after prompt treatment with standard oral antiviral medication: Acyclovir (Zovirax®), valacyclovir (Valtrix®) and famciclovir (Famvir®). None of these promptly eliminate severe shingles pain. Herpes zoster Ophthalmicus (HZO) infections of the eye can cause blindness. The chronic, unremitting pain of postherpetic neuralgia (PHN) can be devastating and incapacitating.

Herpes simplex ocular (HSO) is a rare, but potentially devastating disease. HSO can involve either herpes simplex type 1 (HSV- I) and HSV- II. Superficial HSO can affect the eyelid (blepharo-conjunctivitis) and/or most superficial layer of the cornea (epithelial keratitis) are rather common. HSO stromal keratitis (HSK), endothelial keratitis (endotheliitis) occur less frequently, represent deeper Herpes infection and have significant risks of corneal opacity and blindness. The annual incidence of new and recurrent cases of HSO keratitis is approximately 40,000 to 60,000. In the United States 18% these patients eventually experience one or more recurrences.

Current Standard Treatments

The FDA has approved three drugs for treating Herpes zoster. Acyclovir (Zovirax®), valacyclovir (Valtrix®) and famciclovir (Famvir®) are available as tablets to be taken by mouth. Acyclovir is available as a liquid solution for IV infusion. Acyclovir (800mg) must be taken five times daily. Valtrex (1000mg) is taken three times daily. Both drugs are taken for 7 to 10 days.

If these drugs are started within the first 72 hours after the onset of the rash, treatment reduces the severity and duration of the shingles rash. However, neither oral acyclovir, nor IV acyclovir, nor oral Valtrex are able to immediately reduce the intensity of shingles pain.

In dramatic contrast, the new TELTAB treatment instantaneously eliminates the most intense shingles pain of for 8 to 18 hours or more. Three to 4 consecutive, daily TELTAB treatments typically arrests all progression of the rash.

TELTAB (Tumescent Lidocaine Epinephrine Triamcinolone Acyclovir, vitamin B_{12})

TELTAB (pronounced “Tee-Le-Tab”) is a new treatment for severely painful Herpes infection. TELTAB is intended to treat the most severe forms of Herpes zoster pain. TELTAB treatment consists of the

painless injection of a relatively large volume of the relatively dilute TELTAB solution directly within and beneath the skin affected by the painful shingles rash.

The name **TELTAB** is an acronym for **T**umescent (means swollen and firm), **L**idocaine (local anesthetic), **E**pinephrine (capillary vasoconstrictor), **T**riamcinolone (anti-inflammatory corticosteroid) and **A**cyclovir (anti-Herpes anti-viral drug). Recently vitamin **B_{12}** (an essential agent for health of nerves) has been added to the TELTAB solution. TELTAB may also be effective in treating a Herpes simplex eye infection.

Duration of Herpes zoster Pain

Acute Herpes zoster (AHZ) is characterized by the new onset of intense skin pain caused by the Herpes zoster virus infection. AHZ typically involves 3 sequential stages: 1) abrupt onset of pain affecting a localized area of skin (dermatome) on one side of the body, 2) soon afterward, typically within 1 to 3 days, a rash with vesicles and blisters appears in that same area, and, 3) gradual resolution of the rash over 3 to 4 weeks and complete resolution of the pain over 3 to 8 weeks. Subacute Herpes zoster describes the condition of Herpes zoster pain which persists for more than a month but less than 3 months after the onset of AHZ.

Chronic Postherpetic neuralgia (PHN) is a chronic form of zoster pain that persists for 3months or more. PHN is the most common complication of shingles. In some patients PHN can be severe and incapacitating and can last for years. The risk of developing PHN is increased with age, with impaired immunity, and with inadequate (insufficient or delayed) treatment with shingles-specific oral antiviral drugs. The debilitating pain of PHN often results in impaired physical function and mobility, chronic depression, emotional and physical isolation, and marked reduction in quality of life. PHN also results in significant costs to patients, their care givers and the healthcare system.

Types of Herpes zoster Pain: There are several distinct types of pain associated with nerve injury caused by shingles.

1) Sharp-Stabbing Sudden Pains (Intensity and Frequency can vary)
2) Constant Deep Aching-Burning Pain
3) Pain caused by Light Touch of the affected area (Allodynia)
4) Exaggerate pain caused by a direct touch to the affected area (Hyperalgesia)
5) Constant deep painful itch
6) Persistent bothersome numbness

Tumescent Lidocaine Epinephrine (TEL)

The **TEL (**Tumescent Lidocaine Epinephrine) portion of TELTAB is simply a dilute tumescent solution the local anesthetic lidocaine with epinephrine. TEL immediately produces 8 to 18hours or more of shingles pain relief. TEL is unique in its ability to provide pure sensory regional anesthesia. TEL was invented by Dr. Klein in 1985 for the purpose of performing liposuction totally by local anesthesia. *(Klein JA. The tumescent technique for liposuction surgery. J Am Acad Cosmetic Surg, 1987; 4:263-267).*

Tumescent lidocaine epinephrine (TEL) is also commonly known as tumescent local anesthesia (TLA). Today TEL widely used for many dermatologic surgical procedures and is the worldwide standard of care for procedures several plastic surgical procedures, including tumescent liposuction, facelifts, and breast reductions. In his recent peer-reviewed publication, Dr. Klein has published an objective, evidence-based estimate of the maximal safe dosage of tumescent lidocaine, *(Klein JA, Jeske DR. Estimated maximal safe dosage of tumescent lidocaine. Anesth Analg 2016;122:1350-9*). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4830750/

Components of TELTAB

Dilute Lidocaine in the TELTAB solution is a local anesthetic that provides immediate and profound local anesthesia that completely eliminates Herpes zoster pain for 8 to 18 hours or more.

Dilute Epinephrine in the TELTAB solution produces local capillary constriction in the subcutaneous tissue underlying the painful shingles rash. This vaso-constriction delays the systemic absorption of the TELTAB drugs into the blood stream from under the skin, which thereby prolongs the local effects of all the drugs in the TELTAB solution.

Dilute Triamcinolone is an effective, mid-potency corticosteroid anti-inflammatory drug. The triamcinolone in the TELTAB solution reduces the local inflammatory response to the Herpes zoster virus (HZV), thereby reducing the pain, the blistering, the tissue damage, the nerve injury and the risk of scaring caused by the severe inflammation caused by herpes virus.

Dilute Acyclovir: Acyclovir is an antiviral drug that stops the replication (proliferation) of the Herpes zoster virus, thereby slowing the progression and reducing the intensity of shingles pain and rash. There are three FDA-approved oral drugs for treating shingles: acyclovir, valacyclovir and famciclovir. Valacyclovir is transformed into acyclovir after it is absorbed into the body.

Acyclovir is the only one of these antiviral drugs that is available in liquid form for intravenous (IV) injection. The liquid form of Acyclovir is available commercially at a concentration of 1gm/20ml. Undiluted acyclovir is only approved for IV infusion. Undiluted commercial acyclovir, when injected into or subcutaneously beneath the skin, is toxic to the skin, causing pain and necrosis. The dose of IV acyclovir is limited by an increased risk of kidney toxicity if the mean peak concentration in the blood (and the skin) exceed 20milligrams per liter (20mg/L). When acyclovir is given by mouth or IV, its concentration in both the blood and skin become equal.

The effectiveness of any anti-shingles drug depends on its concentration in the skin at the site of the shingles infection. An ideal acyclovir treatment would maximize its concentration in the skin (to optimize therapeutic effect) and simultaneously minimize its concentration in the blood (to minimize the risk of kidney toxicity). The TELTAB treatment for shingles achieves this goal. By sufficiently diluting a commercial vial of IV acyclovir into a large volume of TELTAB solution and injecting it subcutaneously, the acyclovir concentration in the skin is simultaneously far below the threshold for skin toxicity and far above the concentration that can be achieved in the skin by an IV infusion of acyclovir. At the same time, because of the extremely slow systemic absorption of the TELTAB solution into the blood circulation, the blood level of acyclovir remains well below the threshold for kidney toxicity.

In December 2019, the TELTAB composition was awarded ***US Patent 10493024 B2. Klein. Tumescent infiltration drug delivery of high subcutaneous drug concentrations with prolonged local and systemic effects and minimal local or systemic toxicity (Dec 3, 2019).*** TELTAB uniquely combines the following therapeutic advantages:

1) it is safe when injected subcutaneously,
2) it yields subcutaneous acyclovir concentrations several hundred times greater than can be achieved by IV injection, and
3) it is so slowly absorbed into the blood from the skin that there is no risk of excessive blood concentrations and kidney toxicity.

When acyclovir is given by mouth, the peak acyclovir concentrations in skin is less than 5mg/L. A safe dosage of IV acyclovir yields blood concentrations less than 10mg/L. In contrast, After subcutaneous TELTAB injection, acyclovir concentrations in the skin are 100 times greater in the skin compared to oral or IV acyclovir delivery. It is safe to simultaneously take a standard oral dosage of acyclovir or valacyclovir and also receive daily injections of TELTAB. When TELTAB is combined with oral acyclovir (800mg five times daily or oral valacyclovir (1gm three time daily), the peak acyclovir blood concentration remains well below the peak concentration following IV acyclovir. In most cases of severe acute Herpes zoster pain, two to five TELTAB daily or every-other-day treatments terminates all viral replication, permanently eliminates the shingles pain and stops the blistering rash.

Vitamin B_{12} reduces shingles pain, but the mechanism by which B12 achieves this effect is not precisely known. Vitamin B_{12}, is a water-soluble vitamin involved in the metabolism DNA in every cell of the human body. B_{12} may function by aiding the repair and healing of nerve cells damaged by Herpes virus infection.

Normal saline (0.9% physiologic sodium chloride) is the solvent or vehicle into which the TELTAB drugs are dissolved. By mixing the TELTAB drugs into a relatively large volume of saline, the drugs are relatively dilute, which eliminates the risk of drug-related local tissue toxicity.

All of the other drugs in the TELTAB solution contribute to dramatically reducing the signs and symptoms of acute shingles. Lidocaine provides 8 to 18 hours of complete local anesthesia. Triamcinolone reduces inflammatory damage to the skin caused by the Herpes zoster virus. Acyclovir stop viral replication.

The Volume of TELTAB Solution: The appropriate volume of TELTAB solution varies depending on the area of the body that is targeted for TELTAB treatment. Smaller volumes (50ml to 500ml) are used for the face and scalp. Larger volumes (500ml to 1800ml) have been used on the extremities and the trunk.

Benefits of TELTAB

Acute H zoster pain responds rapidly to a TELTAB injection. In more than 90% of patients TELTAB completely eliminating severe shingles pain (both acute and chronic) within minutes. In the remaining 10% of patients, shingles pain is reduced almost instantly by 75%. Without exception, every patient has confirmed that their decrease in pain is "like night and day." For both acute and chronic (PHN) pain, lidocaine in the TELTAB solution reliably eliminates shingles pain for 8 to 18 hours; many patients get up to 36hours of pain relief. With 3 to 5 consecutive, daily TELTAB treatments, most patients a complete arrest of the acute Herpes zoster rash and at least an 80% reduction in pain intensity. Triamcinolone, acyclovir and vitamin B_{12} make important contributions to the success of TELTAB treatments in permanently eliminating shingles pain. The sooner TELTAB treatments can be initiated the better. For acute H zoster of less than 4days duration, two to four TELTAB treatments can permanently eliminate the pain, and dramatically shorten the healing process. It is important to initiate TELTAB treatment of acute shingles as soon as possible. With delayed treatment, acute Herpes zoster become more resistant to treatment.

PHN pain is more resistant to TELTAB treatment. Nevertheless, some PHN patients can achieve a very significant long-term reduction in pain levels.

Safety of TELTAB

In our experience with TELTAB, the subcutaneous infiltration of tumescent acyclovir is safe and without evidence of any significant adverse effects. Patients who are taking anticoagulant blood thinners such as Xarelto® (rivaroxaban) or Eliquis® (apixaban) may experience bruising at the injection sites.

Subcutaneous Injection of TELTAB is Off-Label

When a specific use of a drug has been approved by the FDA, the "instructions for use" for the drug are printed on a package label that is inserted into each box containing the drug. When a particular use of the drug is not explicitly described on this printed label, the use is considered "off-label".

All of the individual drugs in the TELTAB solution have FDA approval to be sold commercially. However, the combination of these drugs has yet to be approved by the FDA, and therefore a TELTAB solution for treating Herpes virus infection is considered to be "off-label" and cannot be sold commercially. Importantly, the FDA does not object to a physician using TELTAB solution to treat his/her own patients. Similarly, the subcutaneous injection of acyclovir is "off-label".

Because TELTAB is a patented composition, it is illegal for any physician to provide TELTAB and charge a fee for the service unless the physician has a licensed to do so. An FDA requirement for approval of TELTAB to be sold commercially is a clinical trial of TELTAB that establishes safety and efficacy of TELTAB. Dr. Klein is in the process of requesting FDA approval of an Investigational New Drug (IND) application for permission to conduct a clinical trial of TELTAB for treating the most severe shingles pain. In pilot studies of TELTAB for treating shingles Dr. Klein has shown that highly dilute acyclovir solution can be injected subcutaneously without toxicity.

Description of the TELTAB Injection Technique

Dr. Klein has developed the devices and the technique that make it possible to injection of the TELTAB in a manner that is safe, effective, efficient and virtually painless. The "secret" to this painless subcutaneous infiltration of a large volume of TELTAB solution (up to 2.0 liters) is the use of a unique digitally controlled peristaltic tumescent infiltration pump invented and designed by Dr. Klein specifically for ultra-precise

subcutaneous drug infiltration rates. For TELTAB the pump rates can range from an ultra-slow 3ml/min to 200ml/min. The infiltration procedure invented by Dr. Klein utilizes extremely short micro-needles (32gauge or 30gauge). These microneedles are painlessly inserted into the superficial skin while the digital pump is used to inject precise volumes of TELTAB. The result is a number of completely anesthetic (numb) areas or blebs on the skin, one to two inches apart, distributed more or less evenly over the area affected with shingles pain. Next, a slightly larger diameter needle (27gauge, 25gauge or 22gauge) is inserted through the anesthetic blebs in the skin while the digital pump painlessly injects a larger tumescent volume of TELTAB solution into the affected subcutaneous tissue. As an increasing volume of TELTAB solution is injected into an area under the skin, the tissue becomes swollen and firm or tumescent. Because shingles causes the skin to become extremely sensitive to touch, the affected skin must be is treated in a very genTEL manner. With a skillful genTEL technique, the injection process is completed with minimal discomfort. The result of the TELTAB infiltration is complete anesthesia of the treated area. The result is unprecedented. No other technique dependably produces the immediate relief of the most severe shingles pain.

The time it takes to complete a typical TELTAB treatment can range from 15 to 60 minutes, not including the necessary time for preparation before the treatment or the time required afterward for patient care.

TELTAB Treatment Details

For acute Herpes zoster (AHZ), when TELTAB treatments are initiated within four days of the onset of the AHZ pain, usually 2 to 6 treatments are sufficient to prevent all progression of the shingles rash and permanently eliminate more than 80% of the zoster pain. Of course, once blistering has occurred, it takes 7 days or more for the crusted blisters to dry up and fall off. Exceptionally severe cases of shingles may require additional TELTAB treatments. In our experience, prompt treatment of acute shingles with TELTAB significantly reduces the risk of developing chronic PHN or other HZ complications. All acute shingles patients do take the usual anti-shingles tablets (Valtrex, acyclovir or famciclovir) for a total of 10 days.

Subacute Herpes zoster patients have persistent moderate to severe shingles pain which has lasted for more than 8 weeks. These patients often require receive 6 to 10 or more TELTAB treatments before the pain is eliminated. Subacute shingles can be expected to respond well to TELTAB.

Chronic Shingles pain (postherpetic neuralgia PHN):

For chronic postherpetic neuralgia (PHN), TELTAB is less consistently successful. PHN is a chronic disease, similar to diabetes, that can require regular TELTAB treatments once every week or two. A few PHN patients experience long term improvement with only 6 to 12 treatments. For some PHN patients, TELTAB treatments are not sufficiently helpful to justify long term repeated treatments.

Currently there is no reliably effective commercially available treatment for PHN. Furthermore, the drugs that are typically used for this condition often have significant side effects. The current consensus, among those who specialize in treating PHN, is that PHN cannot be cured. However, for some PHN patients, TELTAB can provide definite long-term improvement. PHN is more resistant to TELTAB than acute shingles. PHN patients often receive 12 or more sequential TELTAB treatments, every 4 to 14 days.

If PHN pain has lasted for less than 12 months, there is a reasonable chance that the pain can be completely eliminated. TELTAB shows promise in permanently reducing the intensity and duration of pain in a significant proportion of PHN patients. After a TELTAB treatment, virtually every PHN patient has zero pain for at least 8 to 18 hours or more.

The majority of PHN patients experience a gratifying decrease in pain levels after receiving course of 12 or more TELTAB treatments. Perhaps a third of PHN patients have not had any improvement in response to TELTAB. For some PHN patients, each sequential treatment seems to provide an incremental improvement. TELTAB has permanently cured some PHN patients and in others it has achieved a significant improvement. PHN pain that has persisted for a year or more can be regarded as a chronic disease that requires regular weekly TELTAB treatments in a manner somewhat analogous to diabetes.

It is too early to state that TELTAB will provide a permanent cure for some PHN patients. The initial clinical experience in treating chronic PHN pain is promising. We expect future innovations to improve TELTAB.

Potential Adverse Effects of TELTAB

1) The TELTAB injection is done very gently, nevertheless it does involve touching the areas of the skin affected with shingles. Thus, the TELTAB process does involve some discomfort, but the actual subcutaneous injection of the TELTAB solution is normally associated with no pain or only minimal discomfort.
2) Fleeting episodes skin hypersensitivity and/or pain may occur during infiltration of the TELTAB solution. The vast majority of patients rate the pain of TELTAB infiltration at 0/10 to 1/10.
3) Bruising can occur as the result of the inserting the infiltration needles into the subcutaneous tissue. Bruising is more common among patients who are taking blood thinners, aspirin or anti-inflammatory drugs, and in older patients who regularly bruise easily.
4) Possible adverse reactions to drugs (lidocaine, acyclovir, epinephrine, anti-inflammatory medications) in the TELTAB solution are extremely rare but must be mentioned.
5) Highly dilute epinephrine TELTAB solutions can occasionally cause a brief episode feeling "jittery" which may last for 15 to 30minutes. Dilute epinephrine in the TELTAB solution has the potential to raise the heart rate or the blood pressure briefly for an hour or so. This is unusual at the low dosages used for TELTAB.
6) Any procedure that involves inserting a needle or catheter through the skin may result in infections or injury to blood vessels or nerves. However, this is also extremely rare.

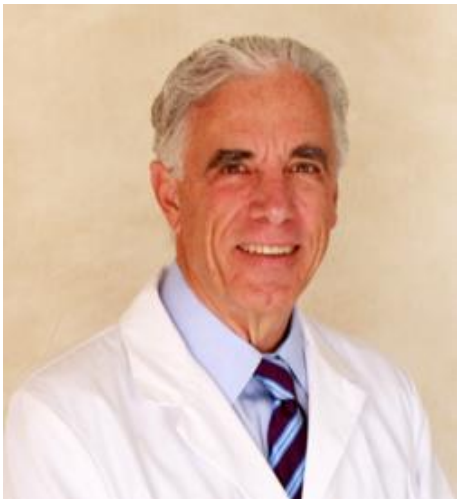

Fig 1. Dr. Jeffrey A. Klein MD

Dr. Klein's Qualifications: TELTAB was invented by Jeffrey A. Klein, MD, whose medical training includes a 2year National Institute of Health (NIH) research fellowship in clinical pharmacology, master's degree in biostatistics (UC Berkeley), certification by the American Board of Internal Medicine (UCLA), and American Board of Dermatology (UC Irvine). On December 3, 2019, Dr. Klein received approval of a United States patent (*US 10493024 B2)* for the composition of the TELTAB solution. Dr. Klein has successfully completed phase-I and phase-II clinical trials of TELTAB. Currently, Dr. Klein is applying for FDA approval of an investigative new drug (IND) application to conduct a formal phase-III clinical trial of TELTAB. The subcutaneous injection of relatively large volumes of tumescent fluid is facilitated by the use of the peristaltic tumescent infiltration pump, developed by Dr. Klein, and widely known as the Klein Pump.