Executive Summary 180314

Tumescent Anesthesia Antibiotic Delivery (TAAD)

A Tumescent Anesthesia Antibiotic Delivery (TAAD) solution consists of a relatively large volume (500ml-1000ml or more) of cefazolin 1gm, metronidazole 500mg, lidocaine 1gm, epinephrine 1mg, sodium bicarbonate 10mEq in a liter bag of saline or lactated Ringer's. Subcutaneous infiltration of a TAAD solution at the site of a proposed surgical incision is a novel mode of antibiotic delivery for prevention of surgical site infections (SSIs) and for reducing post-op pain and opioid requirements. When a relatively large volume of TAAD solution is infiltrated into subcutaneous tissue, the site becomes tumescent (swollen and firm) and results in widespread subcutaneous capillary vasoconstriction and profoundly delayed systemic absorption of the drugs in the solution.

TAAD also refers to our FDA-IND-approved (IND#127921) and IRB (WIRB #20171606) approved multisite randomized clinical trial (RCT). The FDA has never previously approved the subcutaneous delivery of an antibiotic.

Tumescent lidocaine anesthesia (without antibiotics) is remarkably effective in eliminating the pain of acute thoracic Herpes zoster (shingles) for 8 to 12 hours or more. This suggests that tumescent anesthesia ought to provide excellent anesthesia following thoracotomy. However, the vasoconstriction of tumescent anesthesia impairs antibiotic penetration from serum into subcutaneous tissue following IV antibiotic delivery (IVAD) thus reducing the effectiveness of IV antibiotic SSI prophylaxis. TAAD overcomes this limitation by direct subcutaneous antibiotic delivery and subcutaneous antibiotic bioavailability 10 to 100 times greater than achieved by IV antibiotics. [1]

TAAD has a vastly different pharmacokinetic profile compared to intravenous (IV), intramuscular (IM) antibiotic delivery. Tumescent anesthesia was first described in 1985, and first published in 1987.[2] A PubMed search for "tumescent anesthesia" currently returns more than 500 references. tumescent anesthesia is now the worldwide standard of care for endovenous laser ablation of the greater saphenous vein and for liposuction. At a dosage of 28 mg/kg of tumescent lidocaine, the risk of exceeding a serum concentration of 6micrograms/kg, the threshold for mild lidocaine toxicity, is 1 per 5,000,000. [3]

We hypothesize that

1) TAAD plus IV antibiotic delivery (IVAD), that is (**IVAD+TAAD**), is superior to **IVAD** alone for the prevention of SSIs.
2) TAAD will significantly reduce postoperative pain and opioid requirements, accelerate postoperative ambulation and decrease length of stay in hospital.
3) TAAD will reduce the incidence of postoperative venous thromboembolism (VTE) as a result of the antithrombotic effects of local subcutaneous lidocaine concentrations and the constant (zero-order) systemic absorption of lidocaine that resembles of slow IV infusion. This conjecture is supported by our unpublished data.

The randomized clinical trial known as TAAD is specifically intended for preventing SSIs in high risk surgical cases such as dirty-contaminated emergency colonic surgeries, combat casualty care, and all types of surgeries in medically impoverished communities. At present, we are seeking collaborators to join us in conducting the small pilot studies of the TAAD research protocol. We are also seeking grant-funding for the TAAD clinical trial.

There is an interesting possibility that a TAAD solution containing antibiotics but without epinephrine, when delivered by constant subcutaneous infiltration using a SubQKath, may improve antibiotic treatment of necrotizing soft tissue infections based on: 1) greater focal subcutaneous antibiotic bioavailability, 2) improved local tissue perfusion and reduced anaerobic conditions resulting from lidocaine induced capillary vasodilation and 3) reduced small vessel thrombosis and tissue necrosis associated with lidocaine-inhibition of platelet-neutrophil aggregation.

TAAD shows promise in surgically indigent communities where aseptic technique is suboptimal and postoperative analgesia is problematic. In some parts of the world, cesarean-section has a relatively high rate of SSI and virtually no postoperative analgesia. The approximate cost of a 500ml bag of TAAD solution containing lidocaine 500mg, epinephrine 0.5mg and cefazolin 500mg is $12 (US).

See a YouTube video that demonstrates TAAD infiltration:
https://www.youtube.com/results?search_query=Tumescent+antibiotic+Delivery

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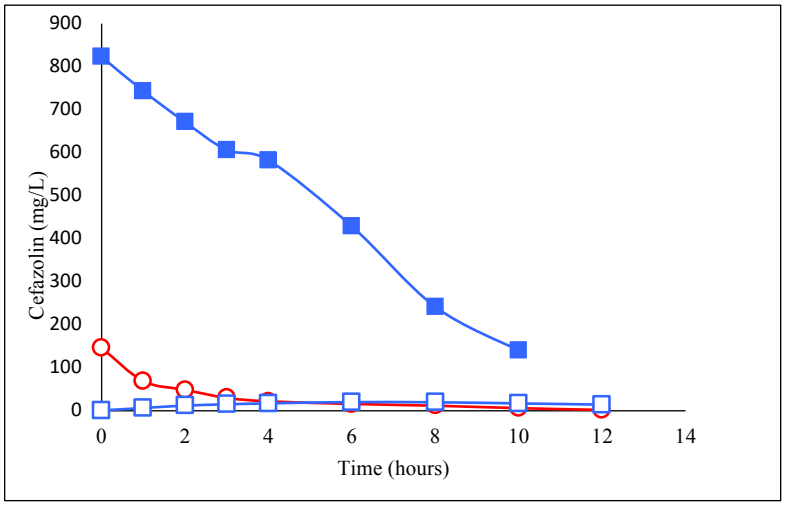
[1] Klein JA, Langman LJ. Tumescent anesthesia antibiotic delivery: pharmacokinetics of subcutaneous cefazolin and metronidazole in a tumescent solution for prevention of surgical infections and biofilms. Plast Reconstr Surg Glob Open 2017;5,e1351.

[2] Klein JA. The tumescent technique for liposuction surgery. J Am Acad Cosmetic Surg, 1987; 4:263-267

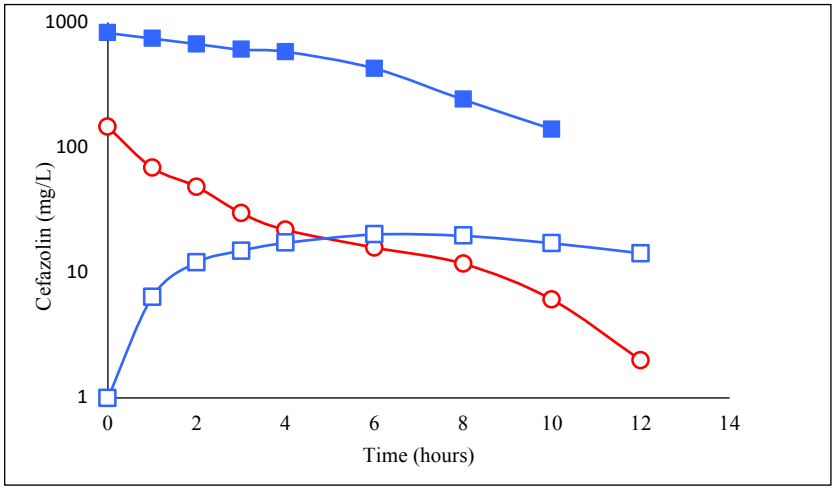
[3] Klein JA, Jeske DR. Estimated maximal safe dosage of tumescent lidocaine. Anesth Analg 2016;122:1350-9.

Concentration-time profiles, IVAD vs TAAD

Comparison of tissue concentration-time profiles following 1gm cefazolin by IV antibiotic delivery (IVAD) and by tumescent anesthetic antibiotic delivery (TAAD).
Open red circles: cefazolin concentrations in serum following IVAD
Open blue squares: cefazolin concentrations in serum following TAAD
Closed blue squares: cefazolin concentrations in subcutaneous interstitial fluid following TAAD.



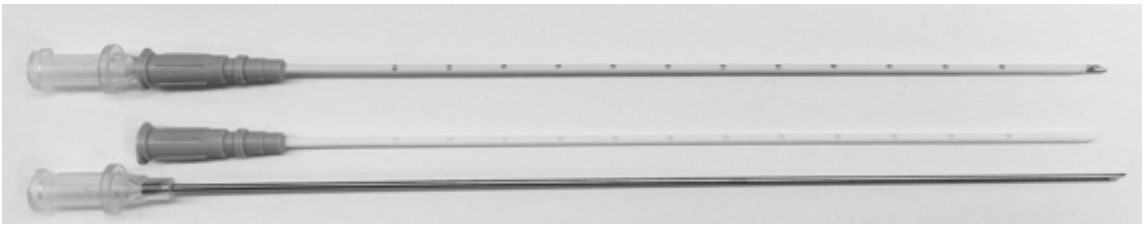
Linear Scale: Cefazolin bioavailability is measured by the area under the curve (AUC) of the concentration-time profile following 1gm cefazolin by IVAD & by TAAD. Following TAAD, the AUC for cefazolin in subcutaneous interstitial fluid is approximately 100x greater than the AUC in serum following IVAD. Following IVAD, subcutaneous concentrations of cefazolin are typically less than or equal to serum concentrations. In obese patients, following IVAD, the AUC for cefazolin in subcutaneous tissue may be 10% of the AUC in serum.

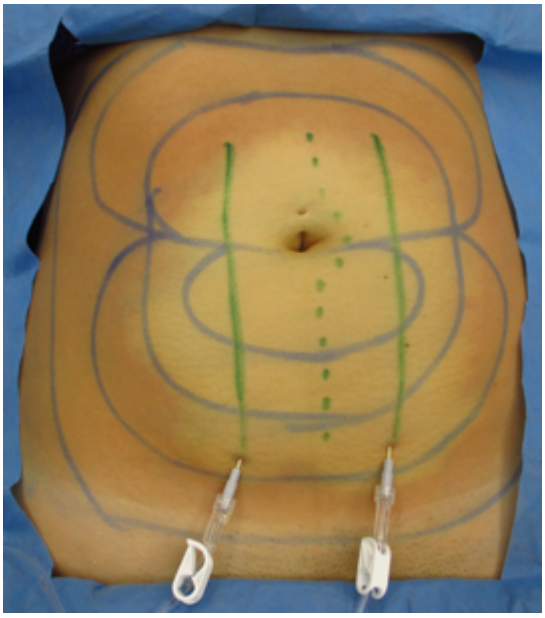


Log-Linear Scale: The concentration-time profile in **serum** following 1gm cefazolin by IVAD & by TAAD is more apparent when the concentration scale is logarithmic. Note that the slow systemic absorption of cefazolin following TAAD results in a **serum** concentration-time profile that closely resembles slow constant IV infusion.

The above pharmacokinetic data suggests that TAAD ought to be significantly more effective than IVAD for prevention of incisional surgical site infections (SSIs). A standard TAAD solution contains cefazolin 1g, metronidazole

500mg, lidocaine 1gm and epinephrine 1mg. The dilute epinephrine produces widespread localized subcutaneous capillary vasoconstriction, which delays the systemic absorption of any drug in the solution. The slow constant (zero-order) drug systemic absorption resembles a constant IV infusion, which for antibiotic SSI prophylaxis may be more effective than bolus IVAD. Following TAAD, the serum Cmax is less than following IVAD, and may have less adverse effect on the gut biome. The lidocaine in the TAAD solution profoundly impairs platelet activation and, in large volume tumescent liposuction, appears to prevent post-op VTE (unpublished data).





Above: The SubQKath is an over-the-needle cannula that is inserted through the skin similarly to a standard IV catheter. The multiple holes distributed along its length allow efficient and painless subcutaneous infiltration of a large volume tumescent anesthetic antibiotic delivery (TAAD) solution.

Left: This clinical photo shows 2 SubQKaths positioned within tumescent subcutaneous fat on either side of a proposed midline incision. Infiltration of 1100ml of TAAD solution produces subcutaneous capillary vasoconstriction, cutaneous blanching and exceptional incision site surgical hemostasis.

Below: The KTP peristaltic tumescent infiltration pump, a liter bag of TAAD solution, and an over-the-needle SubQKath facilitate large volume subcutaneous tumescent infiltration. The SubQKath is inserted through the skin and advanced painlessly while the anesthetic TAAD solution is slowly pumped through the stylet. When the SubQKath is well positioned, the stylet is removed, the infiltration tubing is attached to the catheter, and a liter of TAAD solution is pumped at a rate of 200ml per minute.