160114 A&A Supplement

Supplement 1: an appendix consisting of text documents providing supplemental information for, "**Maximum safe dosages of tumescent lidocaine**"

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A free online PDF version of the 500 page book by Jeffrey Klein, entitled "Tumescent Technique: Tumescent Anesthesia & Microcannula Liposuction" Mosby, St Louis, 2000, is available @ www.tumescent.org. The following information is an update of that book.

Tumescent Safety Tips

1) The maximum recommended mg/kg dosage of tumescent (very dilute) lidocaine and epinephrine without liposuction is 28mg/kg and with liposuction it is 45mg/kg. These dosages do not apply to undiluted commercial lidocaine preparations (0.5%, 1% and 2%) for which the maximum recommended dosage remains 7mg/kg pending further research.

2) Miscommunication between the surgeon and the person mixing the tumescent solution can result in dangerous errors. Unambiguous, legible, written, signed orders are essential for large volume tumescent local anesthesia. The written orders must specify the amount of lidocaine (mg), epinephrine (mg) and sodium bicarbonate (milliequivalents) in each liter bag of tumescent solution.

The amounts of lidocaine in a bag of tumescent lidocaine solution must be specified in terms of "milligrams of lidocaine per bag" rather than "(volume of commercial lidocaine solution) x (% concentration of lidocaine in the commercial solution)". Orders written in terms of (volume) x (% concentration) obscure the actual mg amount and increase the risk of errors and incorrect doses.

For example, an order for "750mg of lidocaine per bag" is simple and concise. For a patient who has received 3 bags of tumescent lidocaine, it is easy to determine the total mg of lidocaine given: 750mg/bag x 3 bags = 2250mg.

In contrast, an order for "75ml of 1% lidocaine per bag" requires more calculation and presents a greater likelihood of miscalculation: 75ml of 1% lidocaine/bag x 3 bags = 75ml x (10mg of lidocaine/ml) per bag x 3 bags = 225ml x 10mg/ml =2250mg.

Orders written in terms of (volume) x (% concentration) also increase the likelihood of a mistaken use of the wrong concentration. The inadvertent substitution of a bottle containing 2% lidocaine when the intention was for a bottle of 1% lidocaine has, on more than one occasion, resulted in excessive dosages of lidocaine.

3) An intravenous access (e.g. heparin lock) is recommended for all patients when the anticipated volume of tumescent lidocaine anesthesia exceeds 1000ml. An established IV access with tumescent anesthesia is most commonly utilized for rapid systemic delivery of atropine (0.3 to 0.5mg) to treat an unanticipated onset of vasovagal syncope or near-syncope. When a vasovagal event is anticipated, atropine 0.4mg IM can be given preemptively. We prefer to use a short 26 gauge needle to load 1 ml syringe with atropine, and then use a 30 gauge 1 inch needle to administer a nearly painless injection.

4) IV fluids are relatively contraindicated with large volume tumescent infiltration because of the hemodilution that occurs following infiltration of large volumes ($\geq$ 3 liters) of tumescent solution. Large volume tumescent infiltration can produce 5-10% hemodilution as evidenced by a transient decreased hematocrit that reverts to pre-infiltration levels within 48 hours. A 75 kg female who received 5 liters of subcutaneous tumescent solution had a transient 10% decreased hematocrit. This "tumescent hemodilution" precludes the use of hematocrit as a measure of immediate post-liposuction surgical blood loss. A large multi-liter volume of IV fluids and a concomitant multi-liter volume of TLA solution may predispose to systemic fluid overload and pulmonary edema.

5) Post-operative orthostatic hypotension following tumescent liposuction is more likely due to effects of drugs or vaso-vagal responses rather than hypovolemia. Post-operative orthostatic hypotension typically responds well to simple observation and small incremental doses of atropine. The incidence of post-tumescent-infiltration tachycardia due to epinephrine effect can be reduced with pre-operative oral clonidine 0.1mg.

Figure S34. Safety labels are applied to both sides of each bag of tumescent lidocaine solution in order to reduce the risk of inadvertent IV delivery.

6) Assiduously avoid inadvertent IV delivery of a tumescent lidocaine solution.   All bags of tumescent solution must be clearly labeled with safety-labels applied on both the front and back of the bag containing tumescent lidocaine solution.   See Figure S34.

7) TLA can be mixed in the operating room immediately before the procedure, thereby allowing the empty and partially empty vials of lidocaine and epinephrine to be set aside and arranged in groups according to bag number. This procedure permits visual confirmation of the proper amount of ingredients in each bag.

8) The person who mixes the ingredients for the TLA solution should be a licensed professional. This person should verbally "call out" each ingredient as it is added to the bag. Furthermore no one should engage in unnecessary conversation with the person preparing the tumescent solution so that there are minimal distractions. Instead of compounding the TLA solution from bottles of plain lidocaine and a vial of epinephrine, one can simply use a commercial bottle of 1% lidocaine with epinephrine 1:100,000; this minimizes the risk of inadvertently omitting epinephrine form the tumescent solution.

9) Avoid drugs that inhibit hepatic microsomal isoenzymes cytochrome P450 3A4 (CYP3A4) and cytochrome P450 1A2 (CYP1A2), which are responsible for the metabolism of lidocaine.

CYP1A2 is inhibited by fluvoxamine (Luvox) and ciprofloxacin (Cipro). CYP3A4 is inhibited by a number of drugs including sertraline (Zoloft), erythromycin, clarithromycin (Biaxin), ketoconazole, fluconazole (Diflucan), itraconazole, amiodarone and closely related drugs [1] Such drugs should be avoided 7 days or more prior to infiltration of relatively high doses of tumescent anesthesia and for 24 hours after infiltration. The mg/kg dosage of tumescent lidocaine ought to be reduced by at least 10 percent for patients who a) have reduced hepatic blood flow (e.g. CHF), b) receive general anesthesia concurrently, c) cannot (or do not) discontinue CYP 1A2 and 3A4 inhibitors or d) have a low plasma protein concentration.

10) Clonidine 0.1mg given orally (PO) immediately before TLA delivery provides anxiolysis without impairing protective airway reflexes. Clonidine also reduces the chronotropic and inotropic effects of epinephrine and clonidine counteracts the tendency for tachycardia and hypertension associated with large volume dilute tumescent epinephrine. Clonidine is not given unless or until the patient's pulse rate > 60 and blood pressure is > 100/60.

11) Prophylactic Atropine, 0.3 to 0.4mg IV or IM, when given pre-operatively for patients with a history of syncope or near-syncope, can prevent perioperative syncope or near-syncope in awake patients undergoing surgery totally by tumescent local anesthesia. Patients who are supine and experience vaso-vagal near syncope typically do not faint but remain alert while experiencing nausea, vomiting and prolonged diaphoresis. This unpleasant and alarming experience can be avoided with the use of pre-infiltration atropine.

12) Warmed tumescent solution (27°C to 37°C) provides patient comfort for infiltration of large volumes of tumescent solution.

13) Avoid ad libitum TLA formulations without substantial clinical and pharmacologic justification. For example, do not add triamcinolone to TLA because of an increased risk of necrotizing fasciitis. [2] Bupivacaine or ropivacaine are more cardiotoxic than lidocaine and unnecessary because the duration of tumescent lidocaine anesthesia is sufficiently prolonged. [3] The addition of sodium bicarbonate to a commercial solution of bupivacaine causes immediate precipitation of bupivacaine, which can cause tissue necrosis if injected subcutaneously. Prilocaine is not recommended because of its association with methemoglobinemia.

14) Anesthesiologist and Surgeon Share Responsibility: The safety of a surgical patient is ultimately the responsibility of all physicians, surgeons, and anesthesiologists in the operating room. If the surgeon is providing tumescent infiltration, then the anesthesiologist must be completely informed about and concur with the total dosage of tumescent lidocaine. An anesthesiologist who is not cognizant of the lidocaine dosage (mg/kg) or the volume of subcutaneously infiltrated tumescent fluid may be unable to prevent adverse drug-interactions or systemic fluid overload. When a patient is given tumescent lidocaine anesthesia, both the surgeon and the anesthesiologist should be familiar with lidocaine pharmacology and tumescent lidocaine pharmacokinetics. [4]

15) It may be safer to use blunt-tipped multi-orifice tumescent infiltration cannulas, rather than standard sharp-tipped infiltration needle, in order to prevent inadvertent intravascular delivery of tumescent lidocaine or puncture of deep structures.

Recipes for TLA Solution

Ingredients in a 1Liter bag of tumescent lidocaine anesthesia (TLA):
● 1Liter bag of physiologic crystalloid solution (0.9% saline or lactated Ringer's solution)
● 50ml to 100ml of 1% lidocaine with epinephrine 1:100,000 (contains 500mg to 1gm of lidocaine and 0.5mg to 1mg of epinephrine)
● 10ml of 8.4% sodium bicarbonate = 10 milliequivalents = 10 mEq

The person who mixes the ingredients for the TLA solution should be a dependable, well trained and experienced. For large volume TLA this person should be a licensed medical professional such as an RN, CNP, PA or MD. This person should verbally "call out" each ingredient as it is added to the bag. Furthermore no one should engage in unnecessary conversation with the person preparing the tumescent solution so that there are minimal distractions.

In order to allow anyone to visually double-check that appropriate amounts of drugs were used in each bag, all lidocaine bottles (empty or partially empty) are neatly collected in separate groups according to the bag number.

The total volume in a bag of TLA solution containing 1gm of lidocaine and 1mg of epinephrine is: 100ml of 1% lidocaine & epinephrine + 10ml Na bicarbonate + 1,000ml saline = 1,110ml. Hence, the concentration of lidocaine in each bag is 1000mg lidocaine/1,110ml saline = 900mg/L = 90mg/100ml = 0.09%. Although this bag of TLA contains 900mg of lidocaine per liter, recording the precise concentration of lidocaine in the TLA solution is not of great clinical importance. It is far more important to know that there is 1000mg of lidocaine **per bag** of TLA solution.

The concentration of lidocaine can be expressed as grams per 100ml (%) or as gram/L. 1% concentration of lidocaine solution = 1gm/100ml = 10gm/L = 10mg/ml. Similarly, 0.1% lidocaine = 1gm/L = 1mg/ml

The concentration of epinephrine can be expressed as grams per 100,000ml or as mg/L. 1:100,000 epinephrine concentration is 1gm/100,000ml = 1gm/100L = 10mg/L =10μg/ml. Similarly, 1:1,000,000 epinephrine = 1gm/1,000,000ml = 1gm/1000L = 1mg/L = 1μg/ml

Instead of compounding the TLA solution from bottles of plain lidocaine and a separate vial of epinephrine, one can simply use a commercial bottle of 1% lidocaine with epinephrine 1:100,000; this minimizes the risk of inadvertently omitting epinephrine from the tumescent solution. However, for some clinical applications, such as liposuction, it may be preferable to add plain lidocaine and epinephrine separately so that the concentration of these two components can be adjusted independently. There are occasions were one might want to minimize the amount of epinephrine given to a patient, for example, a patient with a distant history of a cardiac arrhythmia.

There is a certain risk associated with adding epinephrine separately from lidocaine. If epinephrine is inadvertently omitted from the mixture of TLA, lidocaine will be rapidly absorbed, and perhaps reach toxic serum concentrations.

Adjusting the pH of the solution of tumescent lidocaine by adding 10 mEq of sodium bicarbonate to each liter of solution dramatically reduces the stinging pain of large volume TLA infiltration. Commercially available solutions of lidocaine with epinephrine require a pH of 3.5 to 5 to maximize the shelf life of epinephrine and to increase the aqueous solubility of lidocaine. An acidic solution is painful upon intradermal or subcutaneous injection. This stinging pain can be reduced significantly by adding sodium bicarbonate to the TLA solution and thus shift the pH of the local anesthetic solution toward a more neutral pH. [5][6] A tumescent solution of lidocaine local anesthesia consisting of 500mg to 1,000mg of lidocaine, 0.5mg to 1mg of epinephrine, and 10 mEq of sodium bicarbonate (10ml of 8.4% NaBicarb) in a 1 liter of 0.9% NaCl produces noticeably reduced stinging upon intradermal or subcutaneous injection.

The addition of 10 mEq of sodium bicarbonate is required for both physiologic saline (0.9% NaCl) and lactated Ringer's solution. It is a misconception that Ringer's lactate is buffered and does not require the addition of bicarbonate to neutralize the acidic solution of commercial lidocaine and epinephrine; in fact lactated Ringer's solution only provides bicarbonate after it has been absorbed into the systemic circulation and the lactate has been metabolized by the liver to produce bicarbonate.

TLA Category	Volume of 0.9% Saline	Volume 1% Lidocaine & Epinephrine	Volume 8.4% Na Bicarbonate	Infiltration Device	Infiltration Cannula	TLA Designation
Large Volume	One or more 1000ml Bags	100ml per bag	10ml per bag	Peristaltic pump	Spinal Needle + Monty Cannulas	TLA 1000
Medium Volume	250ml-1000ml	30ml to 100ml	3ml to 10ml	Peristaltic Pump	Spinal Needle + Monty Cannulas	TLA 250 or TA 1000
Small Volume	250ml Bag	30ml	3ml	Syringe or Peristaltic Pump	Spinal or Hypodermic Needle	TLA 250
	100ml Bag	10ml to 30ml	2ml	Syringe	Hypodermic Needle	TLA 100
	50ml Bottle Non-Bacteriostatic	10 ml	1ml	Syringe	Hypodermic Needle	TLA 50
	30ml Bottle Non-Bacteriostatic	6ml	0.5ml	Syringe	Hypodermic Needle	TLA 30

Table S34. The above table describes common formulations of tumescent lidocaine local anesthesia used for surgical procedures involving the skin and subcutaneous tissues.

Caution When Mixing TLA Solution in an IV Bag

It is important that IV bags of TLA solution be labeled with Safety Labels that state "**NOT for IV use**". These Safety Labels are available at www.hksurgical.com. An IV bags is not the ideal TLA reservoir. It is potentially dangerous because of the possibility of an inadvertent attachment to an IV catheter with IV delivery producing acute toxicity. Nevertheless, virtually all TLA solutions are currently mixed in an IV bag for large volume TLA infiltration.

An ideal TLA reservoir bag and TLA infiltration tubing combination would have a unique connector-port so that the spike of a standard IV tube-set cannot be inserted into the TLA reservoir bag. The manufacture of specialized TLA reservoir bags and TLA infiltration tubing with a specialized spike would require a very large market to convince an IV bag manufacturer that producing a specialized TLA reservoir bag is financially feasible. Until TLA is used more widely as a mainstream anesthetic technique, we will have to continue to mix TLA solutions in IV bags while taking extra precautions such as using safety labels and educating OR staff of the potential danger of an inadvertent IV infusion of a TLA solution.

Tumescent Infiltration Techniques

There is more than one way to infiltrate subcutaneous tumescent anesthesia with the patient alert and comfortable. The choice of infiltration technique depends on the relative size of the targeted surface area and the anticipated volume of TLA solution. Painless infiltration of tumescent local anesthesia (TLA) is easily accomplished using techniques that are discussed in detail in this section. None of these techniques is difficult to master. However, a lack of knowledge and skill in these "painless" infiltration techniques may necessitate the use of general anesthesia (GA) or heavy sedation. Ultimately the choice of infiltration technique and the volume of tumescent solution is based on clinical experience.

Only a licensed medical professional such as a registered nurse, physician's assistant or physician should perform large volume tumescent lidocaine anesthesia.

Our preferred method for painless medium-volume and large-volume tumescent infiltration utilizes 1mm adits, spinal needle, blunt-tipped multi-orifice infiltration cannulas and a peristaltic infiltration pump. A painless tumescent infiltration technique can completely eliminate the need for general anesthesia (GA) or heavy IV sedation for many common surgical procedures involving only the skin and subcutaneous tissue.

Tumescent infiltrations are classified as small volume, medium volume or large volume.

Small volume TLA (≤ 250ml) can be accomplished with hypodermic needle or spinal needle and a hand-held syringe. For example, for small volume tumescent anesthesia for dermatologic surgical procedures, a preferred formulation is 10ml to 20ml of 1% lidocaine with epinephrine plus 3mEq (3ml of 8.4%) of sodium bicarbonate in a 50ml bottle of non-bacteriostatic saline. Avoid using bacteriostatic saline for TLA formulation. Bacteriostatic saline contains 10mg/ml = 1% benzoyl alcohol, which can cause local inflammation when injected subcutaneously in relatively large volumes (≥ 10ml).

Medium volume TLA (250ml to 1000ml) can be accomplished with spinal needle (20gauge) or, preferably, with a blunt-tipped tumescent infiltration cannula, together with a peristaltic infiltration pump.

Large volume TLA (≥ 1000ml) is accomplished using 1mm adits, 20gauge spinal needle followed by the use of blunt-tipped tumescent infiltration cannula(s) and a peristaltic infiltration pump.

Typically surgical procedures that only require small or medium volumes of TLA do not require sedation. Prolonged large volume TLA procedures, such as liposuction, are often done with some form of light oral pre-operative sedation such as lorazepam 1mg and/or clonidine 0.1mg. If additional sedation is required, then IV midazolam in 1mg to 2mg increments can be given as needed.

The goal of tumescent local anesthesia is to provide complete surgical anesthesia for procedures involving skin and subcutaneous tissue while improving safety and reducing costs. When a procedure can be done safely and painlessly either by TLA or by general anesthesia, then the patient ought to be given the opportunity to participate in the choice of anesthesia. A patient should not have to receive general anesthesia merely because a clinician does not know how to provide painless tumescent infiltration without general anesthesia. Similarly, a surgery should not be done totally by tumescent lidocaine anesthesia if it would be best accomplished by general anesthesia

For some surgeries, TLA alone may not be appropriate or helpful. For some complex or deeply invasive procedures, general anesthesia or heavy IV sedation plus TLA may be better than either general anesthesia or tumescent anesthesia used alone. The concomitant use of general anesthesia plus TLA can improve the quality of anesthesia. TLA can reduce the amount of general anesthesia or the required depth of general anesthesia. TLA may provide preemptive and

postoperative analgesia, reduce the postoperative narcotic requirements, shorten the time until postoperative ambulation, and shorten the time until discharge.

Figure S35 a,b,c: Large volume painless tumescent lidocaine anesthesia (TLA) of the abdomen for tumescent liposuction totally by local anesthesia, left, pre-operative; middle, immediately after completing tumescent infiltration; right, one day after liposuction. Note minimal post-operative ecchymosis.

Who Can Do Infiltration of Tumescent Local Anesthesia?
Individual state medical boards have rules and regulations that specify who can do injections of local anesthesia including tumescent infiltration. In California, registered nurses, physician's assistants and physicians are typically responsible for doing large volume tumescent infiltration. At a minimum, any accredited office, surgery center or hospital ought to have written policies and procedures that provide guidelines for who can do tumescent infiltration. See www.tumescent.org for an example of written policies and procedures for staff doing tumescent infiltration in a California accredited office or surgery center.
I my opinion, under certain circumstances, a responsible well-trained medical assistant should be capable of doing small volume tumescent infiltration in an office setting while under the close supervision of a physician who is physically present in the same office. However this subject is controversial.
Anesthesiologists typically do not have much experience doing TLA infiltration as a routine procedure. When TLA is done together with general anesthesia (GA), the infiltration is typically done in the operating room by the surgeon immediately before the surgical procedure. When TLA is delivered under GA, the TLA infiltration tends to be done rapidly, with little finesse and it is often incomplete or suboptimal.
Tumescent infiltration in an ambulatory surgical center or in hospital setting can be done prior to the patient entering the operating room or in the OR. In hospitals, tumescent infiltration can be done in a patient's hospital room prior to being transported to the operating room or in a procedure room or in a preoperative preparation area. Large volume tumescent infiltration by an experienced registered nurse or physician's assistant (PA) can be done without the immediate presence of a physician in the procedure room.

When the intention is to do a surgical procedure entirely by tumescent local anesthesia without IV sedation or general anesthesia, then the infiltration technique requires attention to detail and finesse. There are many subtle aspects of painless tumescent infiltration. Even the most competent surgeon or anesthesiologist may find it difficult to do painless tumescent infiltration with some training. A pleasant comforting demeanor on the part of the person doing the infiltration helps to allay a patient's anxiety.

TLA Infiltration Techniques

Many surgical procedures can be accomplished totally by tumescent local anesthesia (TLA) without requiring general anesthesia, heavy IV or IM sedation, or narcotics. The necessary volume of tumescent local anesthesia (TLA) solution depends on the nature of the surgical procedure.

 Small Volume TLA (≤ 250ml) is appropriate for small to medium surgical procedures of skin and subcutaneous tissue such as excision of cutaneous tumors, complex repairs flaps and grafts after excision of a cutaneous lesion, dermatologic laser procedures, complex laceration repairs. Small volume TLA can be infiltrated using 25gauge 2inch long needle or a 20gauge hypodermic needle or a 20 gauge spinal needle together with a syringe. Many common dermatologic procedures can be accomplished with better patient comfort, safety and outcome with relatively small volumes of dilute tumescent lidocaine anesthesia (0.1%) compared to out-of-the-bottle commercial 0.5% or 1% lidocaine with epinephrine.

For example, for small volume tumescent anesthesia for dermatologic surgical procedures, the preferred formulation is 10ml to 15ml of 1% lidocaine with epinephrine (100mg to 150mg of lidocaine with epinephrine) plus 3mEq (3ml of 8.4%) of sodium bicarbonate in a 50ml bottle of non-bacteriostatic saline. See table S34 for formulations of small volume TLA solutions. Avoid using bacteriostatic saline for TLA formulation. Bacteriostatic saline contains 10mg/ml = 1% of benzoyl alcohol as a preservative. Non-bacteriostatic saline is less likely to cause post-operative inflammatory response within infiltrated subcutaneous tissue.

Certain orthopedic surgical procedures that traditionally utilize general anesthesia can be accomplished with tumescent-like anesthetic procedure totally by local anesthesia using 1% lidocaine with epinephrine using lidocaine dosage less than 7mg/kg. [7]

Medium Volume TLA (250ml to 1000ml) is typically utilized for fat harvesting for fat transfer procedures dermatologic surgical excision of a large lipoma, wide excision of a melanoma or non-melanoma skin cancer, excision of large ruptured inflamed epidermal inclusion cysts, debridement and repair of complex lacerations, Hickman Catheter placement **(See Figure S35),** and cardiac pacemaker/defibrillator implantation surgery. Medium volume infiltration is most efficiently accomplished using a peristaltic infiltration pump with a 20gauge spinal needle or a blunt tipped tumescent infiltration cannula.

Figure S36. Tumescent lidocaine infiltrated subcutaneously into right upper chest prior to placement of Hickman Catheter totally by local anesthesia.

Large Volume TLA (≥ 1000ml) infiltration is most efficiently accomplished using a peristaltic infiltration pump together with specialized infiltration cannulas known as Monty cannulas (See below). Large volume TLA infiltration is typically initiated using a spinal needle to provide just enough tumescent anesthesia to allow subsequent painless insertion of blunt-tipped Monty infiltration cannulas. Typically this "small" amount is about 5% to 10% of the anticipated total volume of tumescent lidocaine anesthesia. Monty infiltration cannulas are responsible for infiltration of 90% to 95% of the volume of large volume tumescent lidocaine solution.

Large volume TLA is appropriate for surgeries involving a large surface area of skin, liposuction including fat harvesting for fat transfer procedures, burn surgery, skin grafts, mastectomy, lumpectomy, scrubbing and debridement of large skin abrasion, and endovenous laser ablation of the greater saphenous vein and other vascular surgeries involving relatively superficial vessels. It is not uncommon for liposuction patients to receive large volumes of TLA exceeding 3 to 4 liters.

It is exceedingly tedious to use a manual syringe to infiltrate 250ml or more of TLA by hand, which may cause repetitive motion injury of the hand or wrist. Large volume TLA is most efficient and accurate using a peristaltic tumescent infiltration pump.

TLA infiltration rates of 200ml per minute can be done painlessly and accurately with Monty cannulas. More rapid TLA infiltration (350ml to 500ml per minute or more) can be painful.

Spinal Needle for Tumescent Infiltration

Spinal needles are commonly used for infiltration of tumescent local anesthesia. Small and medium volume tumescent infiltration can be accomplished using a 20gauge spinal needle and a peristaltic infiltration pump. Large volume TLA is accomplished using 1mm adits, 20gauge 3.5inch (0.9mm x 90mm) spinal needle and 16gauge or 18 gauge 8inch blunt-tipped multi-orifice Monty tumescent infiltration cannulas. The 20gauge spinal needle is intended to provide a small but just sufficient amount of tumescent local anesthesia to allow the subsequent comfortable insertion of blunt-tipped Monty tumescent infiltration cannulas. With the help of a peristaltic infiltration pump, blunt-tipped 16gauge and 18 gauge tumescent infiltration cannulas

deliver a much larger volume of tumescent fluid, approximately 90% of the tumescent solution, for large volume tumescent local anesthesia.

A spinal needle easily passes through the fibrous septa of subcutaneous fat and tissue with minimal discomfort to the patient and only a slight risk of injury to subcutaneous nerves or blood vessels. A spinal needle has a non-cutting short-bevel tip designed for puncturing while minimizing the risk of cutting or lacerating vessels or nerves. In contrast, a long-bevel hypodermic needle is designed for cutting through the skin and deeper tissues with minimal resistance, and it is more likely to lacerate tissue.

The technique for using a spinal needle for subcutaneous TLA infiltration has proven to be safe but does require attention to detail. Using a 20 gauge x 3.5inches (0.9mm x 90mm) spinal needle, tumescent local anesthetic solution is injected continuously along a paths radiating outwardly from the point where the needle passes through the skin. A 1mm skin biopsy punch can be used in order to make a 1mm adit or tiny entry hole (see below Stage I: Making Adits) through the dermis and thus facilitate repeated withdrawal and reinsertion of a spinal needle. Adits are used for insertion of blunt-tipped 16gauge Monty infiltration cannulas.

While one hand gently but firmly grips and elevates the skin and subcutaneous tissues, the other hand holds the hub of the infiltration spinal needle and gradually advances the infiltration needle, all the while infiltrating tumescent solution. Maintaining the tip of the spinal needle between the thumb and opposing fingers that grip the skin will minimize any risk of inserting the needle to deeply. As the spinal needle is advanced along a tangential plane, tumescent lidocaine-epinephrine solution is continuously infiltrated using a peristaltic tumescent infiltration pump.

If the area targeted for tumescent local anesthesia is relatively small, then the entire area can be tumesced using a spinal needle. Examples of medium volume tumescent local anesthesia (TLA) procedures that can be done entirely with a spinal needle include: excision of a large lipoma, placement of a cardiac pacemaker or defibrillator (TLA of upper chest superficial to pectoralis muscle), placement of a Hickman Catheter (TLA of chest above pectoralis muscle) or debridement of traumatic wound.

Monty Cannula Technique for Tumescent Infiltration
An ideal or optimal technique for tumescent infiltration is 1) reliably safe, 2) minimizes the discomfort associated with infiltration, 3) minimizes the time required to complete the infiltration, 4) minimizes the total mg/kg dosage of local anesthetic required to produce complete local anesthesia and 5) maximizes the surface area of complete local anesthesia. The following describes the Monty technique for tumescent infiltration, which approaches this ideal.

Figure S37: A Tip Monty, a Half Monty and The Full Monty blunt tipped stainless steel tumescent infiltration cannulas facilitate painless subcutaneous infiltration of large volume tumescent lidocaine anesthesia. The luer lock connector cannula hubs are not shown.

The Monty Infiltration Technique: One of the most effective techniques for infiltrating tumescent local anesthesia uses the combination of Monty infiltration cannulas (HK Surgical, Inc.) and a tumescent peristaltic infiltration pump. This technique involves a four-stage

infiltration process: Stage I: Making Adits, Stage II: initial infiltration using a 20 gauge spinal needle, Stage III: large volume tumescent infiltration using Monty Infiltrators, and finally Stage IV: superficial infiltration and additional tumescent infiltration throughout the targeted area in order to double-check for any "skip-areas" where infiltration might have been insufficient.

Making Dermal Adits: Stage I. The word adit [from Latin adit-us approach, access] is an engineering term that describes a horizontal opening by which a mine is entered, or drained. An adit for tumescent infiltration is a small round hole made by a 1mm skin-biopsy punch that permits easy percutaneous insertion of a blunt tipped infiltration cannula into subcutaneous tissue. 1mm adits typically heal with virtually no visible scar.

Figure S38: A 1mm skin biopsy punch makes 1mm adits, small round holes through the skin, which allow repeated insertions of an infiltration spinal needle and/or blunt tipped infiltration cannulas into the subcutaneous fat without repeated trauma to the dermis. One mm adits heal without visible scars.

For tumescent liposuction there are often two types of adits. For tumescent infiltration 1mm adits are used as openings in the skin for insertion of a 16gauge infiltration cannula. For liposuction 1mm, 1.5mm and 2mm adits allow the insertion of liposuction micro-cannulas for aspiration of subcutaneous fat. Micro-cannulas range in diameter from 18gauge (1.2mm outside diameter) to 12gauge (2.8mm outside diameter). Following liposuction, adits are intentionally not closed with suture in order to allow maximum drainage of the residual postoperative blood tinged anesthetic solution. This drainage reduces postoperative inflammation, swelling, soreness and ecchymosis by allowing elimination of inflammatory fluids.

Adits typically remain open (patent) for as long as there is continued drainage of post-operative blood tinged anesthetic solution. These adits close spontaneously after all post-liposuction drainage has ceased. With effective use of post-operative compression garments, post-liposuction drainage typically stops within 24 to 72 hours. In my experience, infections associated with open adits are virtually non-existent.

Postoperative care of liposuction adits is simple. Patients are instructed 1) to wash the adits (shower) twice daily, beginning the day after surgery, with ordinary bath soap while drainage persists, 2) do not cover adits with bandages or dressings other than super absorbent pads and 3) avoid applying topical antibiotics to adits. In my experience, the application of topical antibiotics to adits is associated with both prolonged inflammation of the skin immediately adjacent to the adit and delayed healing. In addition, topical antibiotics may infrequently be associated with allergic contact dermatitis.

The adits are made as follows. First scrub the targeted area with chlorhexidine gluconate. Then, using tumescent lidocaine solution taken from the TLA bag and a 30gauge 1/2 inch needle, inject small blebs of tumescent local anesthetic solution (approximately 0.5 ml to 1ml) into the dermis and superficial subcutaneous fat. After the injected skin has become blanched (evidence of local tumescent epinephrine effect), the adits are made within each injection site using a disposable 1mm skin biopsy punch.

An alternative to a 1mm round adit is a tiny incision made by a small #11 scalpel blade or a puncture using a 16gauge or 14gauge hypodermic needle (these tiny incisions do not require sutures). There are two minor disadvantages to using tiny incisions rather than round liposuction adits. With a tiny incision there is a tendency for the infiltration cannula to rub and abrade the edges of the tight opening as a result of the to-and-fro movement of the cannula and thereby cause post inflammatory hyperpigmentation. Appropriately sized round adits minimize the incidence of post-inflammatory hyperpigmentation. Another disadvantage, especially when the incisions are used for subcutaneous access for liposuction cannulas, is that tiny incisions heal too quickly, thus preventing adequate post-op drainage of tumescent fluid and increasing the duration of post-op swelling and tenderness, and perhaps facilitating the occurrence of seromas.

Adits heal quickly without being closed with suture. Adits left open do not predispose to infection. Closing adits with suture is associated with increased inflammation and suture induced scaring.

Peristaltic Tumescent Infiltration Pump & Peristaltic Tubing

The peristaltic pump consists of a roller pump and the peristaltic infiltration tubing. Peristaltic infiltration pumps can be a simple device having a brush motor and an analog dial to control the pump rate. More sophisticated peristaltic infiltration pumps have a touch-screen controlled digital stepper motor and very precise control of the pumping rate and roller direction.

Figure S39 A, B: On the left is a basic peristaltic tumescent infiltration pump that has analog controls with a simple variable speed knob. On the right is a more advanced programmable peristaltic tumescent infiltration pump that has touch screen controls and a digitally controlled stepper motor that permits precise selection of pump speeds, a bolus volume option and pumping direction.

The proximal end of the infiltration tubing has a spike-connector that is inserted into the IV bag containing the reservoir of tumescent lidocaine-epinephrine solution.

The infiltration tubing is inserted into the peristaltic roller pumphead assembly. As the rollers turn, the fluid is forced through the tubing. The tumescent solution only comes in contact with the sterile inside of the infiltration tubing. The tumescent solution never comes into direct contact with the pump mechanism. The distal end of the infiltration tubing has a male Luer connector to which a spinal needle or a Monty infiltration cannula can be attached.
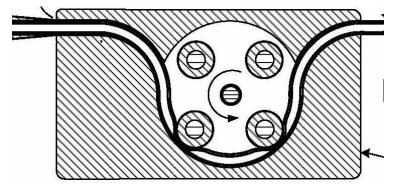
Figure S40: Cross-section view of a pumphead assembly (arrow) for a peristaltic infiltration pump (also known as a roller pump). Infiltration tubing is inserted into the pumphead. The pathway where the tubing is compressed by the rollers is known as the pumphead raceway. The tumescent lidocaine solution is sucked from the reservoir IV bag by the negative suction force generated by the rotating roller assembly. The tumescent fluid flows along the tubing, entering from the left and exiting to the right, under the positive pressure force generated by the rollers.

Initial Purging of Infiltration Tubing

After the infiltration tubing has been attached to the TLA reservoir bag containing tumescent solution, and the infiltration tubing has been inserted into the peristaltic pump-head assembly, the infiltration tubing is purged of air by opening the pinch clamp, turning the pump "on", pumping fluid into the tubing and eliminating any air in the tubing. Once the infiltration tubing has been purged, the pinch-clamp at the distal end of the tubing is closed. Pump is now primed and ready to use. Open the pinch-clamp just prior to beginning infiltration.

Position of TLA Reservoir Bag

When the peristaltic pump is not in use the distal end of the infiltration tubing can be placed on a sterile surgical instrument tray. The more proximal and middle segments of the saline-filled infiltration tubing is allowed to hang or dangle off the tray. In order to prevent the weight of the dangling tubing (which is filled with saline) from pulling the distal end of the tubing off the tray and onto the floor, the male Luer connector at the distal end of the tubing is inserted into the female Luer connector of a sterile 1 inch hexagonal stainless steel weight (www.hksurgical.com). This weight prevents the distal end of the tubing from being pulled off the instrument tray by the heavy saline-filled tubing and onto the floor.

The position (height) of the IV bag reservoir of tumescent solution relative to the surface of the sterile instrument tray is important. When the peristaltic pump is not in motion, the motionless pump rollers may not completely occlude the internal lumen of the tubing. In this situation the hydrostatic pressure within the tubing may cause a very slow flow of fluid (at the rate of a slow constant drip) in one direction or the other through the tubing.

If the IV bag is hung in a position above the surface of the instrument tray upon which the distal end of the tube is resting, there can be a slow leakage from the distal end of the infiltration tubing onto the tray.

If the IV bag is hung in a position below the tray, then the hydrostatic forces may result in a slow retrograde flow of fluid toward the reservoir with a small amount of air entering the distal end of the tubing. This retrograde flow will continue until the air-fluid level in the tubing equals the air-fluid level in reservoir of TLA solution. For certain applications, such as tumescent infiltration for endovenous laser ablation of large varicose leg veins, air in the tubing might be a

problem. When air is injected into the peri-venous tissue it may interfere with ultrasound visualization of the vein. Infiltration tubing is available with a one-way check valve to prevent retrograde flow (HK Surgical, Inc). For most applications, a small amount of air in the tubing as the result of retrograde flow can be ignored. Any air in the tubing can be purged from the tubing before resuming subcutaneous tumescent infiltration.

Spinal Needle Infiltration prior to Monty cannula infiltration: Stage II.

To initiate the infiltration process, a spinal needle is inserted through a 1mm adit, and a relatively small volume of tumescent solution is pumped into the subcutaneous fat along one or more preliminary subcutaneous paths radiating from the adit. This step is repeated using various adits. The relative depth of these preliminary paths is approximately 66% to 75% of the depths of the thickness of the subcutaneous fat. Adjacent paths can be spaced relatively far apart. This initial step is complete when there is a loose network of preliminary paths throughout the targeted area. With experience and attention to detail, a clinician should be able to accomplish the Stage II of tumescent infiltration with little or no discomfort. The goal of this preliminary infiltration is to provide just enough local anesthesia to allow the subsequent painless insertion of larger diameter blunt-tipped 16 gauge Monty infiltrators.

Using one hand to gently but firmly grip and elevate the skin and subcutaneous tissues, the other hand holds the hub of the infiltration spinal needle and gradually advances the infiltration needle while infiltrating TLA fluid, being careful to stay superficial to deep muscle fascia. The tip of the spinal needle is always maintained between the thumb and opposing fingers of the hand gripping the tissue (my left hand), which minimizes the risk of passing the needle too deeply. As the spinal needle is advanced along a plane tangential to deep fascia, tumescent lidocaine-epinephrine solution is continuously infiltrated using a peristaltic pump.

Tumescent Infiltration: Stage III.
Stage III of tumescent infiltration is the most important of the four Stages in the process of providing painless rapid tumescent local anesthesia. Optimal (rapid and comfortable) large volume tumescent infiltration relies on the use of either a single blunt-tipped Monty infiltration cannula or the simultaneous use of two Monty cannulas each attached to a branch of a bifurcated extension tube. TLA infiltration can be done with either a single Monty cannula or two Monty cannulas used simultaneously with one infiltration pump. For tumescent infiltration of a large anatomic area, the simultaneous use of two Monty cannulas and one infiltration pump is very efficient.

Single Monty Cannula Technique: For some areas, it may be easier to simply use a single Monty infiltrator for tumescent infiltration. Using a single Monty cannula together with peristaltic pump infiltration tubing is appropriate for tumescent infiltration of limited areas such as the arms, inner thighs and knees. Alternatively, for more rapid infiltration into larger areas of subcutaneous fat, one can simultaneously use two Monty™ infiltrators together with 2X-extension infiltration tubing with a peristaltic infiltration pump.

The Full Monty and Half Monty infiltrators are 20cm in length and have a unique design.[8] The Full Monty has tiny holes (apertures) distributed along nearly its entire length, sparing only the proximal 2cm of the cannula. The Half Monty has holes distributed along the distal half the cannula. See US Patents numbers 7,914,504; 8,105,310; 8,246,587; 8,506,551; 8,512,292; 8,529,541.

Figure S41: Tumescent infiltration peristaltic pump tubing has a silicone tube portion that is inserted into the peristaltic pumphead roller assembly. The proximal end of the tubing has an IV bag spike and pinch clamp. The distal end of the tubing has a male luer lock connector for attaching an infiltration cannula. The roller compression on the silicone tube creates a proximal vacuum sucking TLA solution into the tubing and a distal elevated pressure driving fluid through the infiltration cannula and into the subcutaneous fat.

For infiltration of large areas, the use of the blunt-tipped Monty cannula is more efficient and safer than the extensive use of a sharp spinal needle. If the area requiring tumescent anesthesia is relatively large, then achieving full tumescent local anesthesia usually requires the use of a full Monty and perhaps a half Monty cannula. Typical examples of large TLA procedures include liposuction, burn debridement, burn donor skin graft harvesting, lumpectomy, mastectomy, or vascular surgery such as endovenous laser ablation of the greater saphenous vein.

The initial step in using a Full Monty infiltration cannula involves inserting the cannula through an adit into subcutaneous fat and then gently advancing it along a path (previously anesthetized with a spinal needle) until the cannula hub is close to or touching the skin adjacent to the adit. In general, this path is at a depth of approximately 66% to 75% of the thickness of the subcutaneous tissue. After the Monty Cannula has been inserted into the subcutaneous tissue, the distal end of the infiltration tubing is attached to the Monty Cannula, the pinch clamp is opened and the peristaltic infiltration pump is switched on. The rate of infiltration should be comfortable for the patient, but not too slow or too fast.

Within a minute or two after beginning the infiltration, the subcutaneous tissue overlying the Monty gradually becomes swollen and palpably tumescent. The patient typically feels a moderate sensation of pressure, which is often described as mildly annoying or bizarre but not painful.

Once there is sufficient tumescence in the tissue surrounding the Monty cannula, the peristaltic pump is turned off, the pinch clamp on the infiltration tubing is closed, the Monty is withdrawn and then re-inserted along a new path at the edge of the newly tumescent and partially anesthetized tissue. After the Monty cannula has been repositioned, the pinch clamp is opened, the pumping is resumed and infiltration continued. After continuing in this fashion, using multiple adits and overlapping paths the entire targeted area of subcutaneous tissue eventually becomes tumesced and anesthetized.

The infiltration tubing has elastomeric properties and expands slightly during under the pressure of the peristaltic pumping. When the pumping stops, fluid continues to flow from the cannula for a few seconds until this elastomeric tubing returns to its resting position. In order to prevent tumescent fluid from spraying out of the cannula as it is withdrawn from the adit, the pinch clamps are closed prior to withdrawing and repositioning the Monty.

Double Monty Cannula Technique: Tumescent infiltration can be done using 2 Monty cannulas concurrently. When the 2 Monty infiltration technique is to be used, the second Monty cannula is inserted through a separate adit, advanced along a separate path and positioned appropriately in the deep subcutaneous fat.   Using 2 Montys simultaneously requires the use of a bifurcated 2X-extension tubing. The 2X-extension tubing allows fluid to be pumped from the single infiltration tubing into two tubes each connected to its own cannula.

       The proximal end of the 2X-extension tubing is connected to the standard tumescent infiltration tubing, which already positioned within the pump and attached to the IV bag reservoir of tumescent solution. The 2X-extension tubing must be purged of air with the pinch clamps open so that the tubing is filled tumescent fluid. After purging the 2X-extension tubing the pinch clamps are closed.
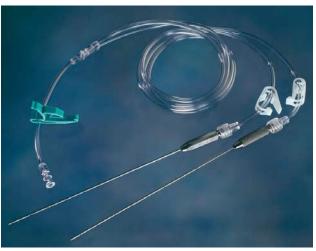

Figure S42: The proximal end of 2X-extension tubing is attached to the distal end of the peristaltic pump tubing. The 2X-extension tubing is bifurcated. The distal ends of the bifurcated tubes have pinch clamps and male luer connectors for simultaneous attachment of 2 Monty infiltrators.

       Next, the 2 distal ends of the 2X-tubing are attached to the two Monty cannulas (previously inserted into the subcutaneous tissue) and one pinch clamp is opened. The clinician starts the infiltration by actuating the pump's remote switch (e.g. a foot-switch).

       While the first Monty continues to infiltrate tumescent solution and the overlying tissue begins to become tumescent, the pinch-clamp of the second Monty is opened so that TLA solution is pumped through both Montys simultaneously.

       Once there is sufficient tumescence surrounding the first Monty, its tube clamp is closed, the first Monty is withdrawn and re-inserted in a different direction through tissue at the edge of the partially anesthetized newly tumescent tissue, and the pinch clamp is reopened. When the tissue surrounding second Monty becomes tumescent, its tubing is clamped, it is repositioned, and its tubing is reopened. In an alternating fashion the two Montys are repeatedly repositioned. In this manner, infiltration is continuous and uninterrupted until all deep levels, mid-levels and superficial subcutaneous tissue planes of the targeted area are more or less uniformly tumescent. Knowing when the endpoint has been achieved is a matter of clinical experience.

Final Superficial Infiltration & Final Touches: Stage IV.

The last stage of tumescent infiltration using the Monty technique utilizes a Tip Monty infiltrator. The Tip Monty has holes limited to the distal 3cm to 4cm of the cannula. At the beginning of Stage IV, it must be assumed that there are small, deep or superficial portions of the targeted tissues that may not have received optimal TLA infiltration, and thus are not 100% anesthetized and not optimally vasoconstricted.

The Tip Monty is passed to and fro throughout the targeted subcutaneous tissue. The patient is asked to alert the clinician if and when the Tip Monty encounters an area of subcutaneous fat that has not been adequately infiltrated and anesthetized. When such a partially anesthetized area is identified, the area is immediately given additional infiltration of tumescent solution. In this sense, the Tip Monty is used to search for possible areas that have initially received incomplete tumescent local anesthesia. In this manner areas of incomplete tumescent anesthesia are quickly identified and efficiently treated.

A superficial area having incomplete infiltration can often be identified by simple visual inspection. An area with less cutaneous blanching compared to the surrounding areas indicates there is less epinephrine-induced vasoconstriction and possibly insufficient tumescent lidocaine anesthesia. Manual inspection by direct palpation can reveal tissue areas having relatively incomplete tumescence in need of a little more tumescent infiltration.

The tumescent local anesthesia is regarded as complete when 1) the targeted area feels more or less uniformly tumescent upon palpation, 2) the skin is more or less uniformly blanched as the result of vasoconstriction from tumescent epinephrine and 3) a little extra tumescent solution has been infiltrated into any areas known to be especially sensitive. Examples of "sensitive areas" on the abdomen that routinely require a little extra TLA are the peri-umbilical area and the fatty tissue overlying the costal margin along the upper abdomen and the lower chest.

During the infiltration process, the Tip Monty is inserted through one adit after another and is methodically passed through the entire targeted tissue until all of the targeted area has been thoroughly "checked" for completeness of the local anesthesia. During this phase, the patient should be alert enough to indicate if and when the Tip Monty encounters an area of insufficient anesthesia. If the patient is a little drowsy then he/she should be aroused and asked to cooperate in this process. The patient is instructed to tell the clinician if and when an area of incomplete anesthesia is encountered. When the Tip Monty encounters an area of incomplete local anesthesia the patient should simply say the word "there." At that point, the area of concern is identified and immediately infiltrated with additional TLA solution until it becomes completely anesthetic.

Upon palpation, if there is a localized area that is insufficiently tumescence, then that area ought to be infiltrated with additional tumescent fluid. If a patch of skin appears to be relatively erythematous due to insufficient epinephrine-vasoconstriction effect then the cutaneous tissue immediately subjacent to that area of skin is infiltrated.

The infiltration process is concluded when the clinician is confident that the entire targeted area has been adequately infiltrated with TLA. After completing tumescent infiltration, the next stage is to allow time for detumescence to occur (see the section below entitled Detumescence).

Other Infiltration Techniques

Many surgeons rely on general anesthesia, or heavy IV or IM sedation, or narcotic analgesia to overcome the pain of rapid large volume tumescent infiltration. The use of general anesthesia allows the surgeon to use a Tip Monty infiltration cannula and to "pump" tumescent fluid into the patient rapidly at a rate that would not be tolerable without systemic anesthesia.

Surgeons who do tumescent liposuction under general anesthesia commonly use this technique. Painless tumescent infiltration is an art requiring gentleness and careful attention to detail.

When TLA is an office procedure, it is common for a nurse to do the tumescent infiltration. This is an efficient arrangement. It permits the surgeon to attend other patients while the nurse does the tumescent infiltration.

Pediatric Tumescent Anesthesia: Most pediatric dermatologic surgical procedures involve relatively small areas and small volume TLA.

In children the most challenging aspect of TLA is overcoming the patient's anxiety and fear of the initial injection of intradermal local anesthesia. A superficial dermal injection of 0.5ml of TLA solution (using a 30 or 32 gauge needle on a 1ml syringe) at the intended site of percutaneous injections ought to be almost painless. Tumescent infiltration is typically done using syringes (e.g. 6ml or 10ml) and a small TLA container (e.g. 50ml bottle of non-bacteriostatic saline 5 ml to 10 ml of 1% lidocaine with epinephrine + 0.5ml sodium bicarbonate). The syringe can be filled using a 20 gauge needle. The subcutaneous infiltration can be done using a smaller hypodermic needle (e.g. 25gauge x 2inch needle or a 20gauge needle).

Another tumescent infiltration technique, slow infiltration tumescent anesthesia (SITA), has been described for routine dermatologic surgical procedures in children and adults[9]. With this technique, a peristaltic pump very slowly transfers the anesthetic solution from an IV bag, through infiltration tubing and into the subcutaneous tissue with one or more hypodermic needles inserted through the skin. With this SITA method, the infiltration is very slow and virtually painless. The down side of this technique is the use of sharp hypodermic needles that, in the setting of a restless or squirming child, may be problematic.

Sources of Infiltration Pain

The pain associated with infiltration of tumescent local anesthesia is largely attributable to four factors:
1) Pinprick pain occurring when injecting the initial blebs for adit placement,
2) Mechanical trauma caused by the insertion of a spinal needle or a blunt-tipped cannula into the subcutaneous tissue and pushing a cannula through non-anesthetized sensitive subcutaneous fibrous septa that partition subcutaneous adipose tissue,
3) Hydrostatic stretching of tissue occurs when a large volume of solution is injected from a cannula with only a small number of holes thus causing rapid painful expansion of a localized volume of adipose tissue, and
4) An acidic pH of the commercial solution of local anesthetic causing chemical irritation when injected into subcutaneous tissue.

The use of a sharp thin hypodermic needle (30 or 32gauge) and the careful gentle technique reduces the first factor.

The skillful use of a spinal needle and then a Full Monty infiltrator essentially eliminates the second and third factors.

Neutralizing the tumescent local anesthetic solution with 10 milliequivalents of sodium bicarbonate per liter bag of TLA solution eliminates the fourth factor.

With a skillful injection technique, one can minimize pain upon insertion of a 30gauge needle when injecting small volumes of TLA into the dermis. Insert the needle slowly, gently into the dermis with the skin stretched taut between the finger and thumb of the hand not holding the syringe. Gently insert the bevel of the needle within the dermis and slowly inject tumescent local anesthetic solution. Continue the injection for a total of approximately 0.3ml to 1ml as the needle is slowly advanced into the superficial subcutaneous fat. After the bleb of intradermal local anesthetic, subsequent needle insertions, incisions, or adit placement at that site are virtually painless. A 30gauge needle can become dull after 10 to 20 injections, and may need to be replaced with a new sharp needle.

When infiltration is done using a spinal needle one can inject the TLA fluid slowly and anesthetize tissue as the needle tip is advanced.

Older infiltration techniques, rely on infiltration cannulas having openings limited to the distal end and require the cannula to be moved in a continuous in-and-out motion and produced rapid local tissue distention as the fluid exited through a small number of tightly grouped holes. Monty Cannulas minimize pain associated with infiltration. Monty infiltrators avoid hydrostatic stretching trauma by dividing a relatively large volume flow of anesthetic solution from many holes spaced along the entire length of the infiltrator. The rate of fluid flowing out of any individual hole is relatively small and therefore relatively painless, while the total rate of fluid injection through multiple holes can be relatively high. Thus a Monty is less likely to cause tissue stretching and pain during infiltration compared to the old style "sprinkler tipped" cannulas or spinal needles at equally large rates of TLA fluid injection.

Detumescence

Detumescence is the time-dependent process during which the degree of tumescence gradually decreases over 1 to 3 hours following tumescent infiltration. Detumescence is an important aspect of TLA that leads to the diminution of the swollen appearance and firm feel of the infiltrated fat. Tumescent local anesthesia can persist for 4 to 6 hours after detumescence has occurred (or 6 to 8 hours after infiltration is completed).

During the process of detumescence, the TLA solution spreads by bulk flow peripherally beyond the initial area of infiltration. Vasoconstriction becomes more wide spread as the local anesthetic solution penetrates into the interstices of the subcutaneous tissue. With detumescence the local anesthesia becomes more uniform and more profound.

A deep incision into tumescent subcutaneous fat immediately after tumescent infiltration reveals subcutaneous tissue with multiple yellow "pearls" of fat embedded within a gelatinous matrix of water-logged interstitial tissue. After detumescence a cutaneous incision reveals fat that looks and feels more "normal".

For some surgeries, such as harvesting donor skin for split-thickness skin grafts, persistence of tumescence facilitates the procedure. However, for most surgeries done under TLA, detumescence facilitates the procedure. For example tumescent liposuction is far easier and much more efficient after detumescence. If liposuction is initiated too soon after completion of TLA infiltration, then the aspirate consists largely of an aqueous infranate of slightly blood tinged TLA solution with only 10 to 20 percent of the aspirate being yellow fat. In contrast after an hour of detumescence the supranatant fat comprises 50 to 70 percent of the aspirate. After two hours or more of detumescence the aspirate will be 70 to 90 percent supranatant fat.

When TLA is infiltrated under general anesthesia, it is not practical to spend an hour or more of valuable operating room (OR) time waiting for detumescence. When TLA is done under general anesthesia there is an incentive to infiltrate a suboptimal volume of tumescent solution. Surgeons tend to infiltrate just enough tumescent solution to achieve adequate vasoconstriction but not enough to achieve adequate local anesthesia.

When liposuction is done under general anesthesia, surgeons tend to avoid full-tumescent infiltration. By using much smaller volumes of a TLA-like vasoconstrictor solution they avoid the need to allow time for detumescence. This modified-tumescent technique sometimes involves infiltrating a fluid containing dilute epinephrine but with little or no lidocaine. [10] [11] The decreased volume of solution infiltrated with this technique results in less intense local subcutaneous vasoconstriction. Liposuction using this minimal volume tumescent technique results in an aspirate containing 8 percent blood [12] compared to only 1 to 2 percent blood [13] in the aspirate with full tumescent local anesthesia. Any reduction of the lidocaine component of a TLA solution will diminish the duration of postoperative analgesia and reduces the antibacterial and antithrombotic effects provided by lidocaine. [14] [15] [16]

In a hospital or surgicenter setting it maybe more practical and economical for TLA infiltration to be performed by a registered nurse or physician's assistant before a patient enters the operating room.

To the extent that tumescent lidocaine has anti-platelet activity, reduced lidocaine concentrations in TLA may reduce the effectiveness of TLA in preventing postoperative venous thromboembolism. Hypothetically, the lidocaine component of the TLA solution may provide multiple benefits including 1) bactericidal properties, 2) prolonged post-operative analgesia 3) reduction of post-operative narcotic requirements, 4) possibly a reduced incidence of post-operative neuropathic pain, 6) breast pain following cancer surgery and 5) inhibition of post-operative platelet aggregation and a possible reduction of the risk of surgery-associated venous thromboembolism.

Care After Tumescent Anesthesia

For almost any cutaneous surgical procedure the combination of preoperative infiltration of tumescent local anesthesia and postoperative physical compression of the wound site dramatically reduces the incidence of postoperative surgical site bleeding, ecchymosis, swelling, tenderness, hematoma and seroma formation.

Tumescent epinephrine produces pharmacologic capillary vasoconstriction lasting at least 6 to 8 hours. Tumescent interstitial pressure from large volume of tumescent fluid produces hydrostatic capillary compression. External physical pressure increases subcutaneous hydrostatic pressure and physically compresses large and small blood vessels. The end result is decreased perioperative bleeding.

Post-Op Compression Reduces Ecchymosis: For post-operative care after a TLA surgical procedure patients wear post-tumescent compression garments and compression binders to improve post-op recovery. For the first few days after surgical procedure under tumescent anesthesia we utilize sterile superabsorbent post-operative pads, placed on the skin over the affected area, to absorb tumescent fluid drainage.

Direct physical compression of a subcutaneous wound increases interstitial pressure and compresses surgically transected capillaries, slows capillary blood flow, reduces the rate of bleeding and the degree of postoperative ecchymosis. Wound compression promotes platelet activation via prolonged platelet exposure to sub-endothelial collagen, facilitates platelet aggregation and early clot formation in traumatized capillaries and small vessels. Wound compression physically stabilizes the early clot, prevents clot disruption and thus supports hemostasis.

Moderate uniform external compression applied to a subcutaneous surgical wound increases the interstitial pressure of compressed tissues. For small cutaneous excisions, direct hand-pressure applied by the patient is usually sufficient to reduce the degree of postoperative bleeding and hematoma. For example, after a small cutaneous excision, direct compression by hand for 15 to 30 minutes is can minimize post-op bleeding and bruising. For a larger procedure such as the excision of a large lipoma or liposuction, the duration of optimal hemostatic-compression for minimal ecchymosis is several hours.

After liposuction, good compression for at least 18 to 24 hours is required in order to maximize the volume of post-operative drainage of blood tinged tumescent fluid and minimize post-operative bruising, swelling and tenderness. Post-op wound compression reduces edema in surgically traumatized tissues by increasing interstitial pressure. This decreases transudation of intravascular fluids into traumatized tissue and promotes lymphatic drainage.

Dermal compression squeezes the gap between collagen bundles in the dermis, restricts migration of erythrocytes to the skin surface, and thus reduces ecchymosis.

Post Compression for Edema Reduction: Tumescent liposuction invariably results in subcutaneous accumulation of residual blood-tinged fluid (drainage) containing tissue fragments, exudative wound fluid and residual tumescent anesthetic solution. Liposuction injures local lymphatic capillaries decreasing resorption of these large molecules. Persistent subcutaneous drainage of blood-tinged tumescent fluid increases interstitial oncotic pressure. This increases trans-capillary exudation of intravascular free-water, increases edema, and predisposes to seroma formation. External compression with open adits produces copious drainage and reduces degree and duration of post-liposuction edema, inflammation and discomfort.

The tiny incisions or adits, through which liposuction-cannula are inserted, provide an effective outlet for post-liposuction drainage. If these incisions are closed with sutures the drainage fluid is trapped inside the subcutaneous wound space. Trapped drainage prolongs the time that a compression garment is needed. Open drainage through open adits (not closed with suture) reduces the need for a compression garment to as little as 2 to 4 days. Open adits also obviate the need for the use of drainage tubes inserted beneath the skin to help eliminate residual subcutaneous fluid.

Sterile super-absorbent post-op pads worn under the elastic compression garments are used in order to control the messiness and discomfort of copious drainage.

With the use of open drainage, super-absorbent pads and compression garments, the post-operative drainage of residual fluid after tumescent liposuction is typically complete within 36 to 72 hours. Patients are instructed to use compression garments and absorbent pads for 24 hours beyond the last evidence of drainage.

The use of compression garments for more than 24 hours beyond the point in time when all open drainage has ceased does not seem to improve long-term cosmetic results. However continued daily use of a compression garment may decrease the degree of swelling that patients experience at the end of each day. For some patients, additional compression provides a sense of security and comfort. Other patients feel encumbered by a compression garment and prefer to be free of compression garments as soon as possible.

Super-Absorbent Post-Op Pads are designed for post-operative care after tumescent local anesthesia. Super absorbent post-op pads are available as sterile pads or as clean (non-sterile) pads. (hksurgical.com) These pads were specifically designed for post-liposuction care where open adits and compression produce copious blood-tinged drainage. Sterile super-absorbent post-op pads absorb large volumes of drainage. Super-absorbent post-op pads can also be used after other surgical procedures.

Super absorbent post-op pads have been designed to prevent leakage of fluid along the edges of the pads when the patient is standing upright or walking. The pads have an inch-wide strip of the impervious water-proof backing that is folded over at the edge of the pad onto the front (absorbent surface) of the pads. This rim or "picture-frame-like" edging prevents gravity-induced leakage of the absorbed fluid when the pad is positioned in a vertical plane. See US Patent 6,162,960. As the fluid is absorbed into the pad from direct contact with the draining adits and patient's wet skin, some of the absorbed fluid percolates downward through the pad under the influence of gravity toward the pad's inferior edge. Upon arriving at the edge, the fluid is "trapped in the trough of the reflected fold and is wicked laterally and back into a less saturated portion of the pad. For example, after abdominal liposuction, when superabsorbent pads are placed on the abdomen, there is minimal leakage beyond the pads when the patient stands upright.

Placing pads on the patient's skin and securing them in place involves several steps. First super-absorbent post-op pads are placed over draining adits. The edges of the pads are often tapped onto the skin with 2inch paper tape to assure optimal contact between the draining adits and the pads. Next, elastic tube netting can be placed over the pads to secure their position. Finally, a post-op compression garment and/or post-op binders are applied on top of the pads and

elastic tube-netting. We prefer this system because it is relatively easy for a patient to change dressings without assistance.

Patients are usually instructed to not remove their postoperative super absorbent pads until the next morning after surgery, before taking a shower. With open adits and effective compression after tumescent liposuction, most of the drainage (> 90%) occurs within the first 18 hours. The drainage typically diminishes to a trickle and then stops within one to three days. Patients are instructed to shower and reapply fresh superabsorbent pads twice daily beginning the day after surgery. Compression garments are to be worn continuously until all drainage has stopped plus an additional 24 hours. Open adits do not increase the risk of surgical site infection.
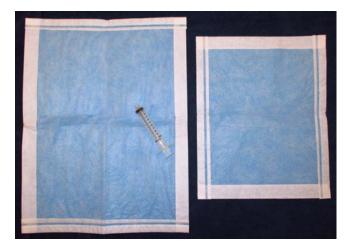

Figure S43: Sterile super absorbent pads can be utilized for containing post-operative drainage of residual blood-tinged tumescent lidocaine anesthesia solution. Maximizing drainage after tumescent liposuction minimizes post-operative swelling, ecchymosis and tenderness.

Tumescent Anesthesia for Other Procedures: First-time cardiac pacemaker implantation, lumpectomy or mastectomy for breast cancer can be done with tumescent local anesthesia.

Pacemaker patients with diabetes, hypertension or antithrombotic medications and lumpectomy patients who have had radiation to the breast are predisposed to postoperative bleeding, ecchymosis, hematoma and seroma. Tumescent anesthesia and postoperative compression decrease perioperative bleeding and decrease the incidence these surgical complications.

In general, the risk of surgical site infection tends to be increased among patients who have diabetes, are on anticoagulants or have had radiation therapy to the surgical site. The use of local tumescent antibiotic delivery (TAD) may decrease the risk of surgical site infections.

Tumescent Antibiotic Delivery (TAD)

TAD is a future application of TLA. A typical TAD solution consists of 1 to 2 grams of cefazolin with or without 500mg of metronidazole in a dilute TLA solution of lidocaine, epinephrine and sodium bicarbonate. A recent pharmacokinetic study of tumescent antibiotic delivery (TAD) of cefazolin and metronidazole showed that the subcutaneous bioavailability of these antibiotics is 10 to 100 times greater compared to equal doses by IV antibiotic delivery (IVAD). Rather than using blunt tipped stainless steel infiltration cannulas TAD utilizes new disposable SubQKaths, which resemble an elongated IV catheter with tiny apertures distributed along more than 90% of catheter's distal end. We hypothesize that pre-operative TAD will decrease the risk of surgical site infections.

Technique for calculating AUC

Area under the curve (AUC) of drug concentration within blood or tissue as a function of time is a pharmacokinetic metric that quantitatively measures the magnitude of tissue exposure to a given drug over time. If drug concentration C(t) can be measured continuously as a function of time t, then

$$AUC = \int_0^{tn} C(t)dt,$$ evaluated from time t = 0 to t_n.

In most cases, concentration is determined at discrete time points [t_0, t_1, t_2, . . . , t_n] in which case AUC can be estimated using the trapezoid rule for discrete sample time points

(1) $AUC = \sum_{i=1}^{i=n} \frac{[C(ti)+C(t(i-1))]}{2}$ (t_i-t_{i-1})

where C(ti) is the drug concentration at time t_i = t(i).

Equation (1) provides a good estimate of AUC[0,t_n], the AUC from time t = 0 to time t_n. For the purpose of comparing the AUCs following different procedures or modes of delivery, it is common to estimated AUC[0,∞] where AUC[0,∞] = AUC[0,t_n] + AUC[t_n,∞].

The concentration of lidocaine from serum after rapid or bolus IV delivery has an exponential rate of decline. In contrast, the rate of elimination of lidocaine from serum after tumescent delivery is approximately a constant. This simplifies the process of estimating AUC[Tn,∞] by determining the area of a triangle having height C(t_n) = (antibiotic concentration at time t_n) and Base = (T_N – t_n) where t_n is the time of the last serum lidocaine measurement and T_N is the graphically estimated earliest time where C(T_N) = 0.

Example of Calculating AUC of Lidocaine Concentration-Time Profile, Without Liposuction, where Bioavailability = AUC(0,24) + AUC(24,∞) = AUC(0,∞) = AUC∞

In the present research, we wanted to calculate the estimated value of AUC∞ for each patient, with and without liposuction. Comparing two AUC∞ results provides a more accurate estimate of the "true" bioavailability than does comparing two AUC(0,24).

The area (A) of any trapezoid is A = B x (H1 + H2)/2, where B is the (magnitude of the base) and (H1 + H2)/2 is the (average of the heights of the two parallel sides).

Consider the area under the curve (AUC) of the lidocaine concentration-time profile from times ti to t(i+1) where the duration of the time interval (ti,ti+1) is 2 hours.

Let f(i) be the concentration at time ti. If the lidocaine concentration is measured every 2 hours, then the area of under the curve between time ti and t(i+1) is
AUC_i = (2hours x [f(2i) + f(2i+2)]/2) mg/ml = 2/2 x [f(2i) + f(2i+2)] = f(i) + f(2i+2) mg-hr/ml.   For example, consider the figure below, where f(6) = 2 and f(8) = 3 then
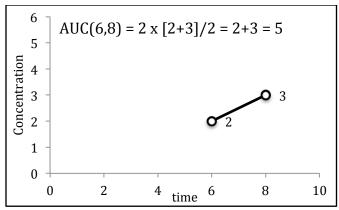AUC(6,8) = 2 x [f(6)+f(8)]/2 = f(6)+f(8) = 2 + 3 = 5

Figure S44. The area under the line from "2 to 3" is simply the area of the trapezoid having base of length 2 (the distance from 6 to 8) and height1 = 2 and height2 = 3. Thus AUC(6,8) = 5.

In the present research design, serum lidocaine concentrations were measured at hours T = 0, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 24.
The area under the lidocaine concentration curve as a function of time from 0 to 24 hours is AUC(0,24) = AUC(0,18) + AUC(18,24).

(1)   AUC(0,18) = Σ Ai = A0 + A1 + … + A8
        = [f(0) + f(2)] + [f(2)+f(4)] + [f(4) + f(6)] + … + [f(14) + f(16)] + [f(16) + f(18)]
        = 1f(0) + 2f(2) + 2f(4) + 2f(6) + 2f(8) + 2f(10) + 2f(12) + 2f(14) + 2f(16)+f(18)
        = f(0) + 2[Σf(2j)] +f(18) for j=1, ..8

(2)   AUC(18,24)   = 6 hours x [f(18)+f(24)]/2 = 3f(18) + 3f(24). Thus
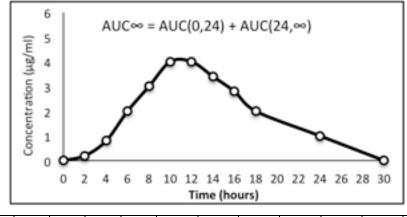
(3)   AUC(0,24) = AUC(0,18) + AUC(18,24)

            = f(0) + 2[Σf(2j)] + 4f(18) +3f(24), for j=1, ..8

This provides a compact (simplified) technique for calculating AUC(0,24) for concentration-time data where the time points were = 0,2,4,6,8,10,12,14,16,18,24 hours. We used this formula for calculating AUC(0,24) for all of the studies for each of the 14 patients. A hypothetical example of this type of calculation is shown below. Note that AUC(24,∞) is the area of a triangle = ½ x height x base, where height = 1 and base = 30-24 = 6. Thus AUC(24,∞) = 3.

See Figures S1 to S14 and Tables S1 to S14.

time (hours)	0	2	4	6	8	10	12	14	16	18	24	30
Height (time)	0	0.2	0.8	2	3	4	4	3.4	2.8	2	1	0

Table 44. Time of serum sample and height of graph (serum lidocaine concentration) following a hypothetical infiltration of TLA.

AUC(0,24)	f(0)	2f(2)	2f(4)	2f(6)	2f(8)	2f(10)	2f(12)	2f(14)	2f(16)	4f(18)	3f(24)	AUC(0,24)	AUC(24,∞)	AUC∞
	0	0.4	1.6	4	6	8	8	6.8	5.6	8	3	51.4	3	54.4

Table S45 and Figure S45: Table S37 above illustrates a hypothetical data set of sequential serum lidocaine concentrations measured over a 24hour interval. Figure S36 shown above illustrates the graph of the serum lidocaine concentrations as a function of time. Table S36 above illustrates how the individual trapezoids f(n) and the cumulative sum of these trapezoids, AUC(0,24), AUC(24,∞) and AUC∞, are calculated using the equations (1), (2) and (3) above.

Toxicity of Lidocaine & Toxicity Thresholds

The threshold concentration for lidocaine toxicity cannot be defined without listing the conditions under which the drug is administered. [17] As the rate of systemic lidocaine absorption is increased, the threshold concentration for the onset of mild toxicity becomes lower. After rapid lidocaine the serum concentration threshold for mild lidocaine toxicity may be 5μg/ml. For slow systemic absorption of lidocaine this threshold may be 6 μg/ml.

The risk of lidocaine toxicity is directly related to serum lidocaine concentration and the rate of lidocaine absorption. The threshold concentration (μg/ml) for the onset of each stage of lidocaine toxicity and the relative toxicity of any given mg/kg dosage of lidocaine depend on 1) rate of systemic absorption [18 19 20 21 22], 2) total amount of lidocaine [23 24 25 26 27], 3) vascularity of the anatomic site of delivery[28 29], 4) mode of delivery (epidural, peripheral nerve block, cutaneous infiltration) [30], 5) rate of metabolism[31], degree of lidocaine binding to serum proteins[32], and systemic oxygenation[33]. Innumerable possible combinations of these factors preclude a precise serum lidocaine concentration threshold for systemic lidocaine toxicity.

As serum lidocaine concentration increases, the manifestations of lidocaine toxicity typically progress through three clinically distinct stages from 1) mild clinical signs and symptoms, 2) to central nervous system (CNS) toxicity and 3) finally to cardiovascular depression and collapse.[34 35] Anticonvulsant drugs such as general anesthesia (GA), propofol or benzodiazepines can mask signs of neurologic toxicity. In this situation cardiovascular effects may be the first objective signs of lidocaine toxicity. [36]

Lidocaine can produce drowsiness.[37] Drowsiness at very low serum lidocaine concentrations is so common after tumescent liposuction that it cannot be considered a clinical warning of impending lidocaine toxicity. Virtually every tumescent liposuction patient becomes drowsy to some extent, even at relatively low mg/kg doses. Patients should not be allowed to drive themselves home after a large volume tumescent lidocaine-epinephrine procedure.

At 45mg/kg of tumescent lidocaine, the incidence of nausea (and, less commonly, vomiting) among liposuction patients is approximately 3% to 5% but the risk of nausea and vomiting is increased among thin (low BMI) patients. The threshold concentration of serum lidocaine for nausea and vomiting is nebulous but we have observed it with a documented serum lidocaine concentration of 2.8μg/ml. Nausea associated with TLA is typically transient, lasting 2 to 4 hours, with onset approximately 8 to 12 hour after completion of the TLA infiltration.

Estimates of serum concentration thresholds for the onset of clinical lidocaine toxicity are based on isolated case reports and animal studies. Classic subjective symptoms of mild lidocaine effects (e.g. lightheadedness, perioral numbness, tinnitus, anxiety, transient color blindness) can occur as low as 4 to 5μg/ml but usually occur above 6μg/ml. With slow systemic absorption of lidocaine, the threshold for objective signs of mild lidocaine toxicity (skeletal muscle twitching, ataxia, nystagmus, slurred speech, confusion, disorientation) is generally considered to be 6.0μg/ml. [38] The onset of significant CNS lidocaine toxicity (e.g. atypical neurologic signs, seizures, coma, apnea) can be expected at 8-12μg/ml. [39] The threshold for cardiovascular toxicity (e.g. bradycardia, hypotension, asystole) is said to be 12 to 15μg/ml. [40 41]

Atypical neurologic signs and symptoms in any patient who has received a local anesthetic should bring to mind the possibility of an inadvertent over-dosage, rapid systemic absorption, or impaired metabolism of the local anesthetic. If the diagnosis of local anesthetic toxicity is not considered early on, then it is often missed or delayed beyond the time where treatment might be effective. Treatment of severe local anesthetic toxicity involves pharmacologic treatment of seizures, adequate ventilation-oxygenation, IV infusion of a 20% soy lipid emulsion and transfer to hospital. [42 43 44 45 46]

Mild lidocaine toxicity is premonitory to serious life-threatening toxicity. In contrast, the onset of bupivacaine toxicity is more worrisome than the onset of lidocaine toxicity because often there is no clinical warning of impending cardiovascular collapse.

Case Reports of Tumescent Lidocaine Toxicity

Case 1. A female patient received 58mg/kg of tumescent lidocaine on two separate occasions for liposuction procedures. With the first liposuction there was no evidence of lidocaine toxicity. Before her second liposuction she began taking sertraline, a potent inhibitor of the hepatic microsomal enzyme CYP3A4 [47]. Twelve hours after her second infiltration of 58mg/kg of TLA lidocaine, she developed mild ataxia and dysarthria with a serum lidocaine concentration of 6.2µg/ml. Symptoms resolved during overnight observation in hospital.

Case 2. Mild lidocaine toxicity occurred following 60mg/kg for tumescent liposuction where the patient denied the current use of any drugs which inhibit CYP3A4. In fact, the night before surgery the patient had finished a 10 day course of erythromycin for an upper respiratory infection. The patient experienced mild lidocaine toxicity with a lidocaine serum blood level of 6.1µg/ml upon admission to hospital. Symptoms resolved during overnight observation in hospital.

Case 3. A female prospective liposuction patient was given a refill-prescription for sertraline by the surgeon at the time of her preoperative examination. Apparently the surgeon, unaware of the sertraline-lidocaine drug interaction, did not tell the patient that she should gradually discontinue sertraline over a two week interval and discontinue sertraline entirely at least one week prior to tumescent liposuction surgery. On the day of surgery she received 76mg/kg of tumescent lidocaine. After completing tumescent infiltration, but before commencing liposuction, she was given an injection of meperidine, which caused intractable vomiting, which in turn forced cancellation of surgery before liposuction. [48] After being discharged home she had a seizure and cardiac arrest. The effects of an excessive mg/kg dosage of tumescent lidocaine, impaired lidocaine metabolism due to a drug interaction with sertraline that inhibited CYP3A4 hepatic enzyme and an increased lidocaine bioavailability because there was no liposuction, all combined to produce a fatal outcome.

Cases 4 & 5. I reviewed two legal cases wherein large mg doses of triamcinolone were added to the solution of tumescent anesthesia under the hypothesis that triamcinolone would reduce postoperative inflammation. Both cases resulted in fatal postoperative necrotizing fasciitis. The surgeons had no objective clinical data to support their hypothesis. Triamcinolone also reduces host defenses against a surgical site infection. Clearly it is not a good idea to add triamcinolone to a TLA solution.

Case 6. An epinephrine overdose occurred in a hospital where regulations required that TLA solutions be prepared in the central pharmacy. Unbeknownst to the surgeon, the pharmacy tech had added 10mg of epinephrine per liter instead of 1mg. The patient survived a subsequent cardiac arrest. It is safer for the TLA solution to be mixed in the operating room shortly before the beginning of the TLA infiltration. TLA should not be mixed the day before TLA infiltration. Furthermore, after each bag of TLA solution is prepared, the empty or partially empty containers of lidocaine (1%) and epinephrine (1:100,000) used for each bag should be lined-up in distinct groups according to the bag number. If there should arise a question about the formulation of any particular bag of TLA solution, the surgeon or a nurse can easily verify that the appropriate quantities of each drug has been added to the bag in question.

Cases 7 & 8. On at least three occasions I have received urgent telephone calls from anxious surgeons asking for advice in managing patients who have inadvertently been given twice the

intended amount of lidocaine. In each case the person mixing the TLA solutions had mistaken used 2% lidocaine instead of 1% lidocaine. I advised observation overnight in hospital. None of the patients suffered serious toxicity. All written orders for lidocaine and epinephrine as solutes in a TLA solution should be specified only in terms of the milligrams (mg) of lidocaine and mg of epinephrine per bag. For example, never specify the amount of lidocaine in term of milliliters (ml) of 1% lidocaine, otherwise an unintentional use of 2% lidocaine instead of milliliters of 1% lidocaine can occur. And according to Murphy's Law this mistake will occur.

Cases 9 to 14. I know of at least five fatal cases of liposuction under general anesthesia where the surgeon did not provide legible written orders for the tumescent solution. In each case the patient probably died from causes unrelated to lidocaine. Many physicians, as well as most lawyers and judges are not cognizant of the unusually safe pharmacokinetic profile of tumescent lidocaine-epinephrine. When a coroner or lawyer is contemplating an unexplained death in a surgical patient who was given a large but unknown amount of lidocaine, the obvious conclusion is criminally negligent homicide due to toxic dosages of lidocaine. Because malpractice insurance policies do not cover legal expenses for defense of criminal negligence, these surgeons had to personally pay for all of their legal defense costs. Careless record-keeping as well as careless surgical practices can lead to bad outcomes. Legible written signed orders for the formulation and delivery of tumescent lidocaine-epinephrine are essential.

Case 15. Bupivacaine should not be used for tumescent local anesthesia. Bupivacaine is significantly more cardiotoxic than lidocaine. [49] [50] [51] [52] It can be very difficult to resuscitate a patient with bupivacaine toxicity. While bupivacaine might provide longer lasting local anesthesia for epidural blocks or regional nerve blocks, there is no evidence that a dilute tumescent-like solution of bupivacaine provides any advantage over TLA with lidocaine. A patient who had cosmetic breast surgery under general anesthesia and lidocaine with epinephrine was also given a postoperative infiltration of bupivacaine in the operating room for additional postoperative analgesia. As she emerged from the effects of general anesthesia in the post-anesthesia recovery room she developed atypical seizure activity. The diagnosis of possible local anesthetic toxicity was not considered until after her condition had progressed to cardiovascular collapse eventuating in permanent brain injury.

Case 16. Because of the greater lipid solubility and very poor aqueous solubility of bupivacaine relative to lidocaine, an acidic solution is required to maintain the solubility of bupivacaine in water. The addition of sodium bicarbonate to a commercial solution of bupivacaine results in an immediate and dramatic precipitation of bupivacaine. One patient (who was also a physician) had an injection of precipitated bupivacaine into her glabella that resulted in local tissue necrosis.
    Cases have been reported of tumescent-anesthesia-associated very early onset of local anesthetic toxicity.[53] Most cases of this nature are likely the result of an adverse reaction to the use of general anesthesia. However, assuming these cases were in fact due to lidocaine effects, the obvious explanation would be an accelerated rate of lidocaine absorption. Potential explanations for such unusual lidocaine toxicity include: 1) inadvertent intravascular (IV) infusion of a bag of tumescent solution intended for subcutaneous infiltration and 2) inadvertent injection into the intra-abdominal cavity resulting in very rapid systemic absorption and 3) the omission of epinephrine from the solution of tumescent lidocaine local anesthesia.

Cases 17 & 18. Omission of epinephrine from the tumescent anesthetic solution results in rapid lidocaine absorption because 1) lidocaine is a capillary vasodilator and 2) because there is no epinephrine-induced vasoconstriction. I know of at least two such events, one of which involved one of my patients. In both cases the patient received approximately 20mg/kg of epinephrine-free very dilute (tumescent) lidocaine. My patient received 18mg/kg of tumescent lidocaine without

epinephrine. She tolerated the event without apparent adverse effects. The apparent Cmax was 2.2μg/ml and the Tmax was at 1 hour or less. See figure S38 below.
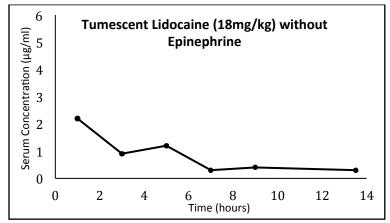

Figure S46. Sequential serum lidocaine concentrations were measured (by HPLC) after the female liposuction patient had inadvertently been given a solution of tumescent lidocaine without epinephrine. Systemic absorption was very rapid, the peak serum concentration Cmax was at least 2.2μg/ml and occurred at Tmax ≤ 1 hour, 10 hours sooner than usual.

Tumescent Pharmacokinetics & Pharmacology

The use of tumescent lidocaine anesthesia permits certain surgeries limited to large areas of skin and subcutaneous tissue to be done entirely without general anesthesia or IV sedation. When combined with appropriate post-operative tumescent compression garments, tumescent anesthesia minimizes the incidence of surgical bleeding, post-operative ecchymosis, hematomas and seromas.

Large volume tumescent lidocaine anesthesia typically provides 6-8 hours of effective surgical local anesthesia. Because lidocaine is well established as both a safe and effective local anesthetic, it is ideal for tumescent local anesthesia. The formulation of tumescent lidocaine anesthesia should not be altered without substantial scientific justification. Higher lidocaine concentrations are rarely necessary for surgery involving skin and subcutaneous tissue. When higher commercial out-of-the-bottle lidocaine concentrations are used the maximum mg/kg dosage of lidocaine is 7mg/kg.

In the present study, at 45mg/kg of tumescent lidocaine without liposuction, there was a difference between the mean AUC∞ among 3 subjects who had infiltration into abdomen and the mean AUC∞ among 5 subjects who had TLA infiltration into hips & outer-thighs. This suggests that different anatomic sites on the trunk and extremities may have slightly different rates of tumescent lidocaine absorption. See Figure S39.
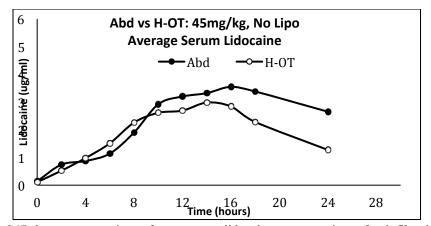

Figure S47 shows a comparison of mean serum lidocaine concentrations after infiltration (without liposuction) of 45mg/kg into abdomen or hips & outer thighs. When a subject had two infiltrations of 45mg/kg of tumescent lidocaine without liposuction, the average concentration for that subject at each time point was used.

The use of percentage (%) to specify the concentration of lidocaine (0.5%, 1%, 2%) in commercial lidocaine preparations, where "1% lidocaine" designates 1gm/100ml or 10mg/ml, can be confusing when calculating the maximum safe volume of lidocaine for a surgical procedure under local anesthesia. We strongly recommend that lidocaine concentrations be given as mg per bag of tumescent solution.

The risk of lidocaine toxicity is low when the rate of systemic lidocaine absorption is slow compared to the rate of lidocaine metabolism. Accelerated absorption or impaired metabolism can increase the peak serum lidocaine concentration (Cmax) and consequently the risk of toxicity.

Lidocaine is metabolized rapidly by hepatic cytochrome P450 (CYP) microsomal enzymes 1A2 and 3A4. Lidocaine has a hepatic extraction ratio of 0.7. Thus for every liter of blood flowing through the liver, 70 percent of its lidocaine content is metabolize.[54] Drugs that inhibit CYP1A2 (fluvoxamine, ciprofloxacin) or CYP3A4 (sertraline, erythromycin, ketoconazole, fluconazole, amiodarone) decrease lidocaine clearance and increase lidocaine

Cmax.[55] [56] Hypotension[57] and decreased cardiac output caused by drugs (propanolol[58], cimetidine[59], and general anesthesia[60]) or diseases (congestive heart failure, hypotension, bradycardia, hypovolemia, hypothermia) can reduce hepatic blood flow and thus slow lidocaine metabolism. For patients who may have significantly impaired lidocaine metabolism, the maximum TLA lidocaine dosage ought to be reduced by at least 20 percent.

After absorption into the systemic circulation lidocaine is rapidly distributed into highly vascular tissues (lungs, skeletal muscles, CNS) and more slowly into less vascular adipose tissue. Because lidocaine is a lipophilic molecule, the volume of distribution for lidocaine is larger in obese patients and smaller in thin patients. Based on our clinical experience, for very thin patients the maximum recommended dosage of TLA lidocaine ought to be reduced by 10 to 20 percent.

In-vitro pharmacodynamic studies of isolated neurons have shown that the ability of local anesthetics to block axonal impulse propagation is a function of both the concentration of local anesthetic and the length of neural axon exposed to the anesthetic.[61] At equal mg/kg dosages of lidocaine, a large volume of dilute TLA lidocaine can produce longer lasting, more extensive and more profound infiltration local anesthesia than small volumes of more concentrated commercial solutions.

With epidural anesthesia the concentration of lidocaine does not affect the magnitude of peak plasma levels [62]. In contrast, with subcutaneous infiltration local anesthesia, more dilute solutions have smaller peak serum lidocaine concentrations.

Subcutaneous infiltration of local anesthesia is unique in that the concentration of the anesthetic solution affects the risk of toxicity. More dilute solutions are absorbed more slowly and therefore are less toxic. For subcutaneous infiltration of lidocaine in mice, the lethal dose (LD50) of 0.5%, 1%, 2%, 4%, 8% lidocaine was 1.07, 0.72, 0.59, 0.42, 0.33 g/kg, respectively. [63] The dilution of lidocaine in a TLA solution contributes to the remarkable safety of TLA.

Lidocaine Clinical Pharmacology: Lidocaine is lipid soluble and therefore it has a relatively high lipid:water partition coefficient. In other words when an amount of lidocaine is added to a mixture consisting of equal volumes of lipid and water, at equilibrium the lipid fraction will contain more lidocaine than the water. Immediately after subcutaneous infiltration most of the tumescent lidocaine is found within the interstitial space or within local adipocytes. Lidocaine is then gradually absorbed into the systemic circulation, redistributed into lipid-rich peripheral tissues.

The rate of systemic absorption of subcutaneous lidocaine is directly proportional to the rate of local tissue blood flow. Intense tumescent vasoconstriction plus lidocaine lipid solubility in adipocytes produce such slow systemic absorption of lidocaine that peak serum lidocaine concentrations typically occur 10 to 16 hours after completion of the tumescent infiltration.

In essence, the absorption pharmacokinetics of subcutaneous tumescent lidocaine is similar to that of a slow or extended release oral tablet. In both instances a large amount of drug is isolated within the body, but the prolonged slow systemic absorption yields a prolonged and relatively low serum drug concentration, and a low Cmax (peak serum lidocaine concentration). Lowering the Cmax minimizes the risk of toxicity. Slow systemic absorption and rapid hepatic metabolism account for the remarkable safety of large mg/kg dosages of tumescent lidocaine.

A large proportion of lidocaine that enters the extra-hepatic circulation is absorbed into peripheral fat deposits and highly vascular tissues. The concentration of lidocaine in the fat and peripheral tissues is in a state of continuous dynamic equilibrium with the lidocaine concentration in blood. Immediately after infiltration the serum lidocaine concentration increases continuously, until it reaches a peak plateau between 10 to 16 hours after completing the tumescent infiltration. At the peak concentration the rate of systemic absorption equals the rate of hepatic elimination. Thereafter the serum lidocaine concentration continuously decreases, reaching zero 24 to 36 hours following infiltration.

Originally developed in the 1940's as a local anesthetic, lidocaine has become as one of the safest and least expensive of all prescription drugs [64]. The maximum safe dosage of lidocaine with epinephrine for infiltration local anesthesia has never been well documented. In the late 1940's clinical investigators established 7 mg/kg as the "maximum recommended dosage of lidocaine with epinephrine" for regional nerve-block anesthesia (continuous caudal anesthesia and spinal and epidural anesthesia). The acceptance of 7mg/kg as the FDA-approved maximum recommended dosage of lidocaine with epinephrine for infiltration local anesthesia was merely the result of a 1948 letter from Astra Pharmaceutical Company to the FDA suggesting that, "the dose recommended for lidocaine is the same as for procaine." In 1949 Gordh recommended a maximum lidocaine dose of 0.5 gm − 1.0gm [65].

In the 1960's the continuous IV infusion of lidocaine was recognized as being effective for controlling ventricular arrhythmias [66] [67]. The range of therapeutic serum lidocaine concentrations for treating ventricular fibrillations was between 1.5 mcg/ml and 5.0 mcg/ml. By monitoring serum lidocaine concentrations of patients on continuous IV infusion of lidocaine it was recognized that mild clinical lidocaine toxicity becomes evident at concentrations exceeding 6.0 mcg/mL [68] [69]. As an aside, IV lidocaine is no longer recommended for shock-resistant ventricular tachycardia. [70]

Lidocaine metabolism is dramatically decreased by anything which decreases hepatic perfusion, such as decreased cardiac output, or impaired hepatic microsomal enzymes CYP1A2 or CYP3A4. Either decreased hepatic perfusion or CYP1A2 or CYP3A4 inhibition will result in a significant reduction in the rate of lidocaine metabolism, increased peak serum lidocaine concentrations, prolonged serum half-life and an increased risk of toxicity.

The onset of lidocaine toxicity is typically associated with relatively mild symptoms of central nervous system excitation such as light-headedness, confusion, dizziness, tinnitus, and blurred or double vision [71]. With increasing lidocaine concentrations (8-10 micrograms/ml) there is a progressive onset of more significant neurological toxicity with atypical seizures. At still higher concentration frank epileptiform tonic-clonic seizures may be seen. Ultimately one sees cardiac depression manifested by bradycardia and hypotension leading to cardiovascular collapse.

Contraindications for lidocaine include: Heart block, second or third degree (without pacemaker), severe sinoatrial block (with pacemaker); history of severe adverse drug reaction to lidocaine or amide local anaesthetics; concurrent use of quinidine, flecainide, disopyramide, procainamide (Class I antiarrhythmic agents) or amiodarone, drugs which inhibit CYP1A2 and CYP3A4, hypotension not due to arrhythmia, bradycardia, or rapid idioventricular rhythm.

Tumescent lidocaine mg/kg dosage ought to be reduced in patients who have impaired or slowed lidocaine metabolism. For example, patients who are concurrently taking drugs which inhibit the hepatic microsomal isoenzymes CYP1A2 or CYP3A4 which are responsible for lidocaine metabolism. Also the mg/kg dosage of lidocaine should be reduced in patients who have a reduced cardiac output and therefore a reduced rate of hepatic blood flow (e.g. congestive heart failure, hypotension, bradycardia, hypovolemia, hypothermia).

Epinephrine mg doses ought to be minimized in patients with a history of significant cardiac arrhythmias, hyperthyroidism or concurrently taking pseudoephedrine or similar drugs.

Adverse reactions to tumescent lidocaine unrelated to mg/kg dosage are rare. Most over-dose reactions to lidocaine are attributable to clinician errors in formulation of the tumescent lidocaine-epinephrine solution or poor administration technique. True allergic reactions to lidocaine are rare and are most often attributable to metasulfite or methylparaben preservative added to multidose vials. Patients who have been told by a dentist that they are allergic to lidocaine often have merely experienced a pharmacologic response to epinephrine injected into highly vascular oral mucosa. In dental anesthesia, a relative insensitivity to lidocaine may be the result of anatomical variation in location of nerves.

Concentration Conversions for Lidocaine (mg/L vs mM)

Clinicians and pharmaceutical companies that sell lidocaine for injection traditionally specify lidocaine concentration as weight per volume of solution (gm/L = mg/ml). a bottle of 1% lidocaine contains 1gm of lidocaine hydrochloride per 100ml of solution (not solvent). The use of the % symbol to designate commercial lidocaine solutions is technically not valid from a purely scientific perspective where % is a dimensionless quantity. But clinicians are not mathematicians. Thus, the convention of designating "1gm of lidocaine HCl per 100ml of solution" by using the short-hand notion "1% lidocaine HCl" is unlikely to fade away. Concentrations of lidocaine HCl for injection local anesthesia will continue to be specified as 0.5% = 0.5gm/100ml, 1% = 1gm/100ml and 2% = 2gm/100ml. For a more detailed discussion, see Wikipedia: "mass concentration".

Clinicians measure serum lidocaine (not lidocaine HCl) concentrations in terms of "micrograms per milliliter" = μg/ml = mg/L. The threshold serum concentration for mild systemic lidocaine toxicity is 6μg/ml. In contrast, non-clinical scientists often specify lidocaine concentration as molecular mass per volume of solution (mol/L = 1M/L).

Thus, when a concentration of a solution is expressed in terms of moles of dissolved substance per liter of solution = mol/L = M/L, the quantitative concentration is referred to as the molarity of the concentration. Note that (1gm lidocaine HCl) ≠ (1gm lidocaine), whereas 1M of lidocaine HCl = 1M of lidocaine.

In order for a clinician to read and appreciate a non-clinical scientific publication, it's helpful to understand some of the confusing subtleties of clinical and non-clinical specifications for drug (lidocaine) concentration. Thus, one must be able to convert gm/L into mole/L. Adding to the potential confusion is the fact that commercial formulations of lidocaine for injection measure the amount of **lidocaine HCl** while lidocaine in serum is measured as **lidocaine (without HCl)**.

A mole of a substance is its molecular weight (mass) in grams. The molecular weight of Lidocaine ($C_{14}H_{22}N_2O$) is 234.34 g/mole and the molecular weight of Lidocaine Hydrochloride is 270.79, where

Carbon: atomic weight = 12g/mole
Hydrogen: atomic weight = 1g/mole
Nitrogen: atomic weight = 14g/mole
Oxygen: atomic weight = 16g/mole
Chlorine: atomic weight 35.45 g/mole

In scientific literature the concentration of lidocaine in solution is specified terms of molar concentration, also called molarity or amount concentration. Molar concentration is a measure of the amount (moles) of a solute in a given volume of solution. A commonly used unit for molar concentration is mole/L, where

1mole/L is also denoted as 1 molar = 1M.
1mM (symbol for millimolar) = 1mM/L

Before lidocaine is injected into the body, the concentration in a manufacturer's formulation is specified in terms of **lidocaine hydrochloride**. In water, a commercial solution of lidocaine is manufactured as 1% lidocaine by adding 1gram of lidocaine HCl (a white crystalline powder) to 100ml of water. The lidocaine molecular formula is ($C_{14}H_{22}N_2O \bullet HCl$) and the molecular weight of **lidocaine HCl** is **270.79 gm/mole** = (234.34 + 35.45 + 1)g/mole.

In commercial formulations the concentration of lidocaine is measured in terms of weight of lidocaine hydrochloride per unit volume. For example, the concentration of commercial out-of-the-bottle lidocaine is typically given as a percentage or weight (gm) per 100ml of solution. For example

1% (lidocaine HCl) = 1gram/100ml = 10gram/L = 10mg/ml (commercial lidocaine)

0.1% (lidocaine) = 1gram/L = 1mg/ml (10-fold dilution for a solution of tumescent lidocaine)

After lidocaine has entered the body, serum concentration is specified in terms of lidocaine (without HCl). In serum, the form of lidocaine that is actually being measured is the lidocaine molecule ($C_{14}H_{22}N_2O$), molecular weight **234.34 gm/mole**.

 The concentrations of lidocaine in solutions of tumescent lidocaine anesthesia typically range from "0.05% = 0.5gm/L" to "0.1% = 1gm/L". In actual practice 1gm of lidocaine is most readily available for clinical use as 100ml of 1% lidocaine with epinephrine. The concentration of epinephrine in commercial local anesthetics is typically specified 1gm/100,000ml = 1:100,000.

 A 1gm/L of a tumescent solution of lidocaine with epinephrine is frequently formulated by adding

100ml of 1% lidocaine + epinephrine (1:100,000) = 1gm lidocaine +1mg epinephrine in 100ml
10ml of sodium bicarbonate (1milliequivalent/ml = 8.4%), plus
<u>**1000ml**</u> of 0.9% saline
1110ml of tumescent solution
where (1gm lidocaine)/1110ml = 0.9gm/1000ml = 0.09gm/100ml = 0.09% lidocaine

1% lidocaine solution = 36.9mM
Lidocaine in a bottle is sold and used clinically as lidocaine hydrochloride (lidocaine HCl). The molecular mass of lidocaine HCl = 270.79g/mole = (234.34 + 35.45 + 1)g/mole.
Thus 1M = 270.79g/L for lidocaine HCl.
 •Commercial one molar concentration of lidocaine HCl = 1mole/L = 270.79g (lidocaine HCl) per L.
 •Commercial 1% lidocaine has a concentration of 1gm/100ml (by definition) = 10g/L = (10g/L) x (mole/270.79g) = 0.0369mole/L = 36.9mM.

0.09% lidocaine in bag of TLA = 3.32mM
A bag of TLA solution solution with a lidocaine concentration of 1gm per bag has a molar concentration of 1gm/1110ml = 1gm/1.110L = 900mg/L = 3.69mM/1.110 = **3.32mM**.

The threshold serum concentration for mild lidocaine toxicity is 6µg/ml = 0.0256mM.
Lidocaine in blood serum is measured as lidocaine, without HCl, which has a molecular weight = **234.34g/mole.** Thus, in serum, 1M = 1mole/L = 234.34g/L. After a little algebraic rearrangement,
1gm/L = 1mole/234.34L = 0.00426 mole/L = 4.26mM, where 1gm/L = 1mg/ml=1000µg/ml. Thus
 4.26mM = 1000µg/ml or
 4.26mM/1000 = 1µg/ml = 0.00426mM.
Hence **6µg/ml** = 6 x (1µg/ml) = 6 x 0.00426mM = **0.0256mM**

Some Speculation about TLA Effect on Platelets
 After subcutaneous infiltration of tumescent lidocaine anesthesia for liposuction, the concentration of lidocaine in subcutaneous interstitial fluid is approximately equal to the lidocaine concentration in a bag of tumescent solution, which is **3.32mM.**
 The **3.32mM** of lidocaine in TLA solution is far in excess of the serum concentration threshold **0.0256mM** for systemic mild lidocaine toxicity. However the mean peak serum lidocaine concentration (mean Cmax) after a 45mg/kg dosage of tumescent lidocaine is approximately **0.012mM**.

This observation has clinical relevance. Tumescent lidocaine anesthesia may impede systemic platelet activation and reduce the risk of venous thromboembolism. Lidocaine inhibits platelet-leukocyte aggregation at concentrations of 1-3 mM and may thereby reduce systemic inflammatory responses to surgery. [72]

At serum lidocaine concentrations ≤ **0.0256mM**, lidocaine has very little effect on platelet function. However, after prolonged (≥ 1-2 hours) of platelet exposure to **3.32mM** lidocaine, platelet activation, aggregation and degranulation seem to be significantly impaired. [73]

By inhibiting platelet degranulation at the site of surgical trauma, TLA may reduce the systemic pro-thrombotic effect of surgical trauma associated massive exposure of platelets to sub-endothelial collagen. Furthermore it is plausible that the prolonged exposure of circulating platelets to low concentrations of systemic lidocaine following TLA can inhibit some aspects of systemic platelet function. We hypothesize that large dosages of tumescent lidocaine may reduce the risk of venous thromboembolism (VTE) and reduce systemic inflammatory responses to surgical and other forms of trauma. It is well established that TLA virtually eliminates surgical bleeding associated with liposuction. However it is noteworthy that the incidence of VTE following tumescent liposuction totally by local anesthesia is essential zero. On the other hand, the leading cause of death associated with liposuction under general anesthesia is pulmonary embolism.

Ancillary Medications with TLA

There are three medications that are commonly used in conjunction with tumescent liposuction: clonidine, lorazepam and atropine. These drugs may be useful for other surgical procedures (without liposuction) done totally by tumescent local anesthesia.

Clonidine is an effective antihypertensive drug with two well-recognized side effects: sedation and bradycardia. These side effects limit the usefulness of clonidine as a medication for outpatient treatment of hypertension. However, with TLA these pharmacologic features are beneficial. Clonidine (0.1mg PO) is an effective anxiolytic without respiratory depression. The tendency of clonidine to cause bradycardia counteracts the tendency for large volume tumescent lidocaine-epinephrine to cause tachycardia. Caution: do not exceed the 0.1mg PO dose of clonidine. Clonidine is primarily useful for counteracting the tendency of epinephrine to induce tachycardia. Giving more than 0.1mg of clonidine for sedation can result in post-operative orthostatic hypotension and a delayed discharge.

Lorazepam (1mg) has long lasting anxiolytic effects. Unlike other benzodiazepines it is not metabolized by hepatic microsomal isoenzymes CPY 1A2 or CYP3A4, and therefore does not competitively inhibit lidocaine metabolism. In addition, lorazepam has potent antiemetic effects that counteract the nausea and vomiting which occasionally occur with higher doses of tumescent lidocaine.

Atropine, when given as 0.3 to 0.4 mg IM or IV, is effective in preventing vasovagal events among patients with any history of vasovagal syncope or near-syncope. This is particularly useful when a surgery is to be done totally by local anesthesia with the patient fully awake and alert. Prior to any tumescent lidocaine procedure, the patient is asked if he or she has any history of fainting or near-fainting. All patients with a history of fainting or near fainting are pre-medicated with 0.3 to 0.4 mg of atropine given IV or IM. This preemptive approach is more than 95% effective at preventing vasovagal reaction.

FDA & Economic Aspects of 7mg/kg

For a number of commonly performed surgical procedures, tumescent lidocaine anesthesia (TLA) is safer, more effective and less expensive than general anesthesia. There are two issues which seem to hinder the wider use of TLA: 1) the inappropriately low 7mg/kg dosage limitation for TLA which is imposed by the antiquated and unscientific FDA regulations concerning lidocaine for infiltration local anesthesia, 2) the absence of CPT billing codes for TLA which effectively precludes the use of TLA by anesthesiologists wishing to be reimbursed for their services

There is considerable evidence that 7mg/kg is an unnecessarily low dosage limit. Several million patients have had tumescent liposuction with dosages of 35mg/kg to 55mg/kg of tumescent lidocaine far exceeding 7mg/kg, but without evidence of toxicity. To date it has been exceedingly difficult for an individual or group of individuals to petition the FDA to change the 7mg/kg restriction. Because lidocaine is a generic drug there is little financial incentive for a pharmaceutical firm to invest its time and resources in seeking change in the 7mg/kg limitation. Thus the 7mg/kg limit continues to restrict the use of TLA and promotes the use of general anesthesia for surgical procedures where TLA would clearly be safer, more comfortable and less expensive.

The situation is especially frustrating because the FDA has absolutely no scientific evidence to support the 7mg/kg limit of lidocaine with epinephrine for infiltration local anesthesia. In 1948, when the FDA approved lidocaine for local anesthesia, the only data provided to the FDA for establishing the maximum recommended mg/kg dosage of lidocaine was derived from epidural and nerve block procedures. There was no data derived from subcutaneous infiltration of lidocaine and epinephrine. In 1948 the assumption was that cutaneous surgical procedures rarely require more than 7mg/kg of lidocaine with epinephrine and therefore it would not be necessary to validate the limit with clinical data. (See www.tumescent.org).

However with the advent of TLA and the collection of objective pharmacokinetic data, it is now apparent that 7mg/kg is not merely low, but may be dangerously low. The unnecessarily low 7mg/kg dosage limit, encourages anesthesiologists to use general aesthesia in situations where TLA would be less dangerous, less expensive and more effective. Anesthesiologists eschew TLA because of their reluctance to use anesthetic drugs in an off-label fashion. If lidocaine labeling were to be updated based on modern clinical experience and research, then anesthesiologists might be more inclined to provide TLA. Furthermore, TLA would be eligible for new CPT codes, thus allowing reimbursement for TLA.

There are no AMA approved CPT codes for TLA. Without CPT code for TLA, anesthesiologist cannot get insurance reimbursement for doing TLA. Without reimbursement for providing tumescent anesthesia, some anesthesiologists, hospitals and surgical facilities will be reluctant to provide tumescent anesthesia. CPT codes for TLA will never be created until tumescent lidocaine dosages are no longer off-label. Thus until the FDA changes its 7mg/kg restriction, there will be no CPT codes for TLA and anesthesiologists will be less likely to use local tumescent lidocaine anesthesia.

Tolerance Intervals

Definition: confidence interval

  A 95% confidence interval is an interval based on a random sample that yields bounds for an unknown population parameter such as the population mean μ. If the random sample is repeatedly computed, then 95% of the confidence intervals will contain the true value of μ. A confidence interval cannot predict the value of a future observation, nor can it tell us anything about the percentage of the population having values below a certain threshold.

Definition: prediction interval

  A prediction interval based on a random sample provides bounds for one or more future observation from a sampled population. A prediction interval cannot estimate the percentage of the population having values below a certain threshold.

Definition: tolerance interval

  A tolerance interval is an interval, based on a set of sample data, which is designed to contain a specified proportion or percentile (P%) of all future observations with some stated confidence. [74] [75]

  We can specify that a tolerance interval contain **P%** of the population and also specify the degree of confidence of, say, 95% or 99%, that the tolerance interval does indeed contain P% or the population. Then, given a random sample of **size n** from a much larger population, we can calculate the bounds of the tolerance that satisfies our specifications. A higher specified degree of confidence requires wider tolerance interval.

  In our research, we specified a 99% degree of confidence in our tolerance interval estimates. For example, after specifying that we wanted to have 99% confidence in our results, we found that among all non-obese female patients given 28mg/kg of tumescent lidocaine without liposuction, 99.99998% of the population (all but 1/5,000,000 of the population) would have a peak serum lidocaine concentration (Cmax) less than 6μg/ml. In other words, at 28mg/kg of tumescent lidocaine without liposuction, the risk that Cmax $\geq$ 6μg/ml is 1/5,000,000.

  Thus, with a high degree of confidence, our data demonstrated that at 28mg/kg of tumescent lidocaine there is a very small probability of mild lidocaine toxicity. The actual magnitude of our estimated probability of toxicity is not important. What is important is that our data clearly demonstrates that tumescent lidocaine anesthesia at 28mg/kg without liposuction and 45mg/kg with liposuction represents a non-significant risk for harm to patients.

  Confidence intervals and tolerance intervals are different concepts although both are based on a set of data from an individual sample. In least-square linear regression analysis a confidence interval is concerned with describing the accuracy of an estimate of the true population mean. For example, a 95% confidence interval of a true population mean has the interpretation of that if a large number of same sized samples were taken from the same population then 95% of the corresponding confidence intervals would contain the true population mean. A confidence interval does not provide any information about future individual observations.

  In contrast, for a tolerance interval, we must specify both the desired degree of confidence (or assurance) and the proportion (or content) of all future individual observations which one wants to be contained within the interval.

  For example, in the present research, we might have chosen to have 95% confidence that 999 out of a 1,000 (99.9% content) of all future observations would lie below an upper tolerance limit B_U (upper bound) Then based on our sample data we could calculate B_U and state that we have 95% confidence that the probability that any future observed value will exceed B_U is less

than 1/1000, or equivalently, that 999/1000 observations would have a value (e.g. Cmax) smaller than B_U.

In the present research, we specifically chose to use a 99% confidence level. Furthermore, we wanted to find the largest content level that would result in a value B_U less than or equal to 6μg/ml, the threshold for mild lidocaine toxicity. We proceeded, using an iterative process of trial and error, as follows. At a given mg/kg dosage of TLA lidocaine, say 40mg/kg without liposuction, we specified an initial content of 99/100 and then calculated the corresponding tolerance upper bound B_{U1}. If this B_{U1} was less than 6μg/ml, then we would tentatively specify a larger content, say 999/1000, and again calculate the corresponding B_{U2}. If B_{U2} was still less than 6μg/ml, then we continued the process. If, at content 9999/10000, we found that B_{U3} was very close to but less than 6μg/ml, then we would report 9999/10,000 as the content level for 40mg/kg. The interpretation of this calculation would be that, at 40mg/kg we could have 99% confidence that 99.99 percent of future determinations of Cmax would be less than 6μg/ml. Equivalently, we could state that 40mg/kg of tumescent lidocaine is associated with a risk of less than 1/10,000 that Cmax > 6μg/ml. The entirety of Table 1 was constructed in this manner. As an example, it can be read from Table 1 that based on our data, at 40mg/kg we have 99% confidence that the risk of Cmax exceeding 6μg/ml would be 1/750 without liposuction and 1/15,000 with liposuction. In this manner we arrived at the estimate that at 28mg/kg without liposuction the risk of lidocaine toxicity is one per 5 million.

Given the variation of Cmax at a given mg/kg dosage, tolerance intervals answer the question, "What is the probability that P% of all future Cmax will fall within defined acceptable limits?" For our tolerance interval analysis we confirmed that all inputs were normally distributed with a variance proportional to the dosage level by examining residuals, that individual observations are statistically independent and that there is a linear relationship between the variables under consideration.

The use of tolerance intervals in pharmacokinetic studies to assess the risk of drug toxicity as a function of dosage is not commonly encountered in the clinical literature. A tolerance interval approach to clinical toxicology has more intuitive and compelling validity than the common practice of merely stating the average dosage and range of dosages together with the rather absurd conclusion that the range of dosages is safe because no toxicity was observed.

R-Code to Compute Upper Tolerance Bounds from Regression

```
# This is R code to compute upper tolerance bounds from regression
# where the variance of the errors are proportional to the x-variable.
# Derivation of the formula for the tolerance bound follows that in
# Krishnamoorthy K, Mathew T. Statistical Tolerance Regions. John Wiley & Sons, New
# Jersey, 2009, which considers a similar type of heteroscedastic variance.
# The data used in this example is the no liposuction data.
# Through an iterative process, changing the content value, we arrive
# at Content = 749/750 as the value that produces 6 ug/ml as the
# 99% confidence upper tolerance bound when the dosage is 40 mg/kg.
# The output of this code is a scatter plot of x vs. y, the fitted
# least squares line, and the fitted upper specified confidence
# tolerance bounds that have the specified content.

library(MASS)

x<-c(35.1,31.2,25.1,45,45,22.5,38.7,22.5,45,20,19.4,45,45,22.5)
y<-c(3.4,2.1,2.7,3.6,3.2,1.4,2.7,1.9,4.2,1.6,1.6,4.4,3.7,1.8)

plot(x,y,xlab="Dose",ylab="Peak",xlim=c(10,60),ylim=c(0,8))

Confidence<-0.99
Content<-749/750

alpha<-1-Confidence
beta<-1-Content
n<-length(x)
xmat<-cbind(rep(1,n),x)
D<-diag(x)
Di<-solve(D)
bhat<-solve(t(xmat)%*%Di%*%xmat)%*%t(xmat)%*%Di%*%y
s2<-(t(y)%*%(Di-Di%*%xmat%*%solve(t(xmat)%*%Di%*%xmat)%*%t(xmat)%*%Di)%*%y)/(n-2)
abline(bhat[1],bhat[2])
tbounds<-NULL
x0vals<-seq(10,60)
 for (x0 in x0vals) {
  xvec<-matrix(c(1,x0),2,1)
  hx<-t(xvec)%*%solve(t(xmat)%*%Di%*%xmat)%*%xvec
  kappa<-qt(1-alpha,n-2,qnorm(1-beta)*sqrt(x0)/sqrt(hx))
  tbounds<-c(tbounds,t(xvec)%*%bhat+kappa*sqrt(s2)*sqrt(hx))
}
lines(x0vals,tbounds,col=2)
lines(x=c(10,60),y=c(6,6),lty=2)
lines(x=c(40,40),y=c(0,6),lty=2)
```

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