PROTOCOL SUMMARY

Study Format
This study will be a pilot, single center study

Describe the aim of the study
The global aim of this study is to investigate how microneedles can enhance the penetration and efficacy of topical anesthesia.

Research methods/Procedures:
The studies will be conducted on the right and left ventral forearms of the research subjects. Each subject will serve as his own control. The right forearm and the left forearm will be randomized through a binary randomization to determine whether the right arm will receive microneedle treatment or sham microneedle treatment (roller with no microneedles). This randomization is developed through code in Excel that will result in binary result of either the value 0 or 1 for each subject. For those subjects assigned a binary code of 0, the right forearm will receive microneedle treatment and the left forearm will receive sham microneedle treatment. For those subjects assigned a binary code of 1, the left forearm will receive microneedle treatment and the right forearm will receive sham microneedle treatment.

The forearms will then be treated with an FDA approved topical anesthetic. The topical anesthetic used will be topical 4% lidocaine (ELA-Max, also known as LMX4). The different treatment sites will have four different times of incubation based on the treatment sites. After the appropriate incubations (2 min, 5 min, 10 min, and 30 min), the topical anesthetic will be removed and each of the treatment sites will receive a standardized pain stimulus through the use of the needle lancet. After each treatment site pair receives the pain stimulus, the subject will be asked to rate their pain on a 100 mm visual analog pain scale.

If applicable, address how the study will involve the use of drugs, devices, biologics, or radioactive materials (both FDA approved or investigational):
Topical 4% lidocaine is FDA approved for use as a topical anesthetic. The PI (Raja Sivamani) has experience with the use of microneedles and has conducted and published previous human clinical studies with microneedles (Sivamani RK *et al.*, Clinical microneedle injection of methyl nicotinate: stratum corneum penetration. *Skin Res Technol.* 2005; 11(2):152-6.)

Pre-sterilized microneedles will be used with each subject. The MTS Roller^{TM} MR2 (200 micrometers in length) is available from Clinical Resolution Laboratory, Inc. The microneedle pretreatment will consist of rolling the microneedle roller or the sham microneedle roller on the skin at each treatment site. The microneedles are rolled in 8 different directions over the treatment site.

Specify the nature, frequency and duration of research procedures
Each of the subjects will be asked to wait in a quiet room for 15 minutes with minimal activity to allow their blood flow and body temperature to calibrate to the ambient temperature. The subject will then have the sham microneedle or the actual microneedle pretreatment to the right and left forearm as outlined previously in #2. The patient will then undergo incubation with topical anesthetic for a total of 30 minutes and then receive the pain stimuli as described previously. The patient is required to be present for only one visit and no follow up is required. The entire procedure is estimated to take a total of 1 hour for each subject.

State from where subjects will be recruited, when and how many.
The subjects will be recruited from the existing patient base at the UC Davis Department of Dermatology, the student population at the undergraduate campus at the University of California – Davis, and the student population at the Sacramento State University campus.

Specify the age of the research subjects.
The research subjects will be from 18 to 60 years of age.

List all criteria for including and excluding subjects.
Inclusion criteria: All subjects that are male, 18 to 60 years of age, and do not meet any of the exclusion criteria.
Exclusion criteria: Subjects who smoke or have a previous allergy to topical or injected anesthetics.

If women and minorities are excluded, provide rationale for such exclusion.
Minorities will not be excluded. However, we are excluding women from this particular study as previous data suggests that women have a higher pain tolerance than men to the same pain stimuli (Spierings EL *et al*., Two-minute skin anesthesia through ultrasound pretreatment and iontophoretic delivery of a topical anesthetic: a feasibility study. *Pain Med.* 2008; 9: 55-59). As such, the use of men would better delineate any differences between the sham and the actual microneedle stimuli. The inclusion of women in the subject pool would add an additional confounder that would affect the power of the study to detect a difference between the two treatment groups.