UNIVERSITY OF CALIFORNIA

Los Angeles

Does phentolamine mesylate reverse soft-tissue anesthesia after 3% mepivacaine?

A thesis submitted in satisfaction

of the requirements for the degree of Master of Science

in Oral Biology

by

Andreia Minasian Silvera

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ABSTRACT OF THE THESIS

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Professor Steven Ganzberg, Co-Chair

Professor Renate Lux, Co-Chair

In this randomized, double-blind, sham-controlled study the investigators evaluated the efficacy and safety of phentolamine mesylate (PM) in shortening soft-tissue anesthesia after intraoral 3% mepivacaine without vasoconstrictor inferior alveolar mandibular block. A total of 44 subjects received one or two cartridges of 3% mepivacaine plain local anesthetic using a standard injection technique to achieve profound lower lip anesthesia, followed 30 minutes later, in the same location and in a blind fashion, by either PM or sham injection (in which the needle does not penetrate the tissues) using the same technique and in a 1:1 cartridge ratio. The subjects were observed for four hours

during which duration of soft tissue anesthesia and oral function were evaluated, oral exams were performed and vital signs were recorded. The median time to recovery of normal sensation of the lower lip after PM/sham injection was 160 minutes (±13 min) in the sham group and 95 minutes (± 12 min) in the PM group, for a reduction in duration of numbness of 65 minutes (41%) in the PM group as compared to the sham treatment groupWe did not observe a statistically significant reduction in recovery time for the tongue, nor a hastened return to normal oral function as compared to the subjects who received sham injections. Additionally, PM appeared to be well tolerated, with no clinical adverse effects.

The thesis of Andreia Minasian Silvera is approved.

Igor Spigelman

Diana V. Messadi

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BACKGROUND AND SIGNIFICANCE

Phentolne mesylate (PM), 4,5-dihydro-2-[N-(*m*-hydroxyphenyl)-N-(*p*-methylphenyl) aminomethyl]-1*H*-imidazole 1:1 methanesulfonate, is a non-selective alpha-adrenergic antagonist, with vasodilator effects on vascular smooth muscle and some direct positive inotropic and chronotropic effects on cardiac muscle (1). Phentolamine has a duration of action of 10 - 15 minutes (2) and a half-life of 19 minutes after intravenous administration. It is metabolized by conjugation or hydroxylation conjugation and excreted in the urine, but approximately 13% of a single intravenous dose appears unchanged in the urine (1). Its clinical indications include control of pheochromocytoma-associated hypertension, treatment of dermal necrosis following drug extravasation, and treatment of erectile dysfunction. In the past, PM was also utilized to diagnose pheochromocytoma via the phentolamine blocking test. Contraindications include myocardial and coronary artery disease and hypersensitivity to the medication, while common side effects include hypotension and reflex tachycardia. More recently (2009) phentolamine mesylate has been available in dentistry marketed as OraVerse® (0.4 mg phentolamine mesylate in 1.7 ml dental cartridges) for reversal of soft-tissue anesthesia following injection of a local anesthetic with vasoconstrictor. After intraoral administration, phentolamine reaches peak plasma concentrations within 10 - 20 minutes and has a terminal elimination half-life in the blood of 2-3 hours (Novalar). Although the mechanism by which OraVerse® accelerates reversal of soft-tissue anesthesia is not fully understood, it is believed that competitive inhibition of administered vasoconstrictor with resultant vasodilation leads to increased local blood flow enhancing the clearance of the administered local anesthetic agent from the site of injection, thus more quickly reversing neural blockade (3).

The current literature contains several studies on the efficacy and safety of phentolamine mesylate reversal of local anesthetics that contain vasoconstrictors (4,5,6,7). Many dentists, however, including pediatric dentists and other dentists who see children in their practices, as well as dentists who treat patients with medical conditions restricting the administration of epinephrine, utilize local anesthetics without vasoconstrictors, predominately 3% mepivacaine plain. The untoward effects of lingering soft-tissue anesthesia in these situations can lead to trauma to the lips and tongue, particularly in young children. Soft tissue anesthesia, such as to the lip and tongue, can last approximately 3 hours when dental local anesthetics without vasoconstrictors are utilized for inferior alveolar nerve block (8). The use of PM to successfully reverse soft tissue anesthesia in this circumstance remains unaddressed therapeutically. While PM is postulated to antagonize the effects of the vasoconstrictor contained in dental anesthetic cartridges, the investigators entertained the idea that PM, via its vasodilatory or other non-adrenergic properties (9,10), could also enhance the redistribution of the local anesthetic itself away from the site of injection, thus hastening the return of soft tissue normal sensation. The purpose of this study was to determine the efficacy and safety of phentolamine mesylate in shortening soft-tissue anesthesia after intraoral 3% mepivacaine without vasoconstrictor inferior alveolar mandibular block.

SAMPLE SIZE DETERMINATION

Utilizing previous studies, a needed sample size of 20 subjects per treatment group was calculated based on a treatment effect difference of 70 minutes (5), a standard deviation of 88 minutes, an alpha error of 0.05 (one-sided test) and a beta error of 0.2. Because it was predicted that up to 10% of subjects might not show complete reversal of local anesthesia at the end of the 4-hour study period, the sample size was increased to 22 per group.

MATERIALS AND METHODS

This randomized, double-blind, sham-controlled study was approved by the Human Research Protection Program of the University of California, Los Angeles (UCLA) Institutional Review Board (UCLA IRB # 11-002473).

Subjects were recruited via flyers placed in the UCLA School of Dentistry and the Electronic Bulletin Board as well as through personal communication. Subjects were offered compensation of $200 for time spent participating in this project and a gradually decreasing amount should they stop participating at other times prior to completion of all planned procedures. After a preliminary screening interview done either telephonically or in person, forty-four potential subjects were recruited and randomized via a random number generator utilizing an Excel spreadsheet to receive either phentolamine mesylate or sham injection following inferior alveolar nerve block.

All subjects had to be at least 18 years old; American Society of Anesthesiologists (ASA) Physical Status I or II; have no contraindications to the study medications; have not taken non-opioid analgesics or opioid medications within 24 hours prior to study; have negative urine pregnancy test at screening (all females except those whose menstrual periods had not occurred for >1 year after menopause, who had been surgically sterilized, or had had a hysterectomy); have normal lip and tongue sensation and function at screening; have the ability to understand and give informed consent; and have the ability to understand, follow and comply with study instructions. Volunteers were disqualified from participating in the study if they had any contraindicating oral conditions, such as an oral soft tissue lesion or oral pain that might adversely affect study results; had used any investigational drug and/or participated in a clinical study within 30 days of this study; had any condition which, in the opinion of the investigators, increased the risk to the subject of participation in this study or decreased the likelihood of compliance with the protocol; were pregnant, lactating, or unwilling to use contraception or abstinence for 2 days after study; or were unable to attain lip soft-tissue anesthesia after having received two cartridges of local anesthetic using a standard inferior alveolar technique as administered by highly experienced dentist anesthesiologists.

Recruited subjects were seated in a dental chair at the UCLA School of Dentistry Children's Dental Center or adjacent Advanced Treatment Planning Clinic, where medical and oral history as well as inclusion and exclusion criteria were reviewed by study investigator #1. After determining that the volunteer met all the inclusion criteria and none of the exclusion criteria, the IRB-approved consent to participate in the study

was reviewed and signed. A copy of the signed consent form and investigator contact information was then given to the participant. Women at risk for pregnancy (see above) were required to have a negative beta-human chorionic gonadotropin (β-hCG) urine test (Wondfo). Subjects were then fitted with an automated non-invasive blood pressure cuff and pulse oximeter (Passport 2, Mindray Corp.) and baseline vital signs (heart rate and blood pressure) were taken and recorded. A visual intraoral examination was then performed to assess for any soft tissue lesions in the proposed mandibular quadrant. Subjects were then given instructions and training on the soft tissue sensation rating assessment and Functional Assessment Battery (FAB) and baselines were obtained and recorded. Specifically, for sensation training of the lip and tongue, subjects were asked to tap the lip or tongue three times in rapid succession with the pad of a finger using light pressure and to rate the sensation as numb (no feeling), tingling (a sensation that is like pins and needles), or normal. All baseline lip and tongue sensation, per inclusion criteria, had to be normal. For FAB, the subjects were asked for a big smile and any baseline asymmetry of their smile was noted; then they were asked to read three sentences aloud to assess baseline speech articulation. The three sentences were:

- Suzie sews zippers on two new dresses at Bessie's house.
- She usually rushes to push the garage door closed.
- Ruth caught a cold because she wouldn't wear her new, warm, wool coat.

The FAB consisted of measures of smiling, speaking (reading aloud the three sentences), presence or absence of drooling, and assessment of uninterrupted drinking of 3 oz. of water. An interim FAB (iFAB), in which the drinking was omitted, was used during the time when the lip and/or tongue were subjectively deemed numb by the subject.

At this point one of two UCLA dentist anesthesiologists (investigators #2 or #3) were introduced to the volunteer, and, using a cotton applicator, applied 20% benzocaine topical anesthetic gel, bubble gum flavor (Patterson), to the proposed injection site, allowing it to remain in contact with the mucosa for 1 minute. After wiping the topical anesthetic with dry gauze, one cartridge of 3% mepivacaine without vasoconstrictor (Scandonest®) was administered by the same dentist anesthesiologist utilizing a standard inferior alveolar nerve block technique and time was recorded. Subjects were then asked to rate the lower lip numbness, and, if at 10 minutes after the initial injection profound lip numbness had not been obtained, a second inferior alveolar block of the same local anesthetic was administered by the same dentist anesthesiologist. An oral cavity assessment was performed by investigator #1 after profound lip numbness was obtained by visually inspecting the intraoral mucosa at and near the injection site. At 25 minutes after the last local anesthetic injection an oral exam was performed, lip numbness was confirmed, sensation rating and interim FAB were administered (smiling and speaking tests, and noting any presence of drooling), and both the investigator and the subject rated each of the tests as either normal or abnormal; the results of these tests were recorded. At this point investigator #1 left the vicinity of the subject, and the same investigator who administered the local anesthetic to the subject (i.e., investigator #2 or #3) placed a visual barrier over the subject's eyes (an opaque eye mask to obstruct the subject's view of the syringe of study drug and the needle cap), and at 30 minutes after the last intraoral local anesthetic injection, per pre-defined randomization scheme, administered either PM or

sham (where the injection needle did not penetrate the tissues) at the same intraoral location, and employing the same technique used for the local anesthetic administration, and in a 1:1 ratio with the volume of local anesthetic administered (i.e., subjects who required one cartridge of local anesthetic received one cartridge of PM/sham, and subjects who required two cartridges of local anesthetic received two cartridges of PM/sham). Completion time was recorded. For the next four hours investigator #1 performed and recorded soft tissue sensation rating and iFAB every 5 minutes (assessing for symmetry of smile, slurred or abnormal speech while reading the three sentences, any drooling), until the time when sensation of the lip and tongue as well as iFAB returned to normal, at which time final FAB (including drinking of water) was performed and recorded. Additionally, investigator #1 obtained and recorded oral exams and vital signs every 10 minutes for the first 30 minutes, and then at 30 minute intervals. Any adverse effects were noted and recorded. Before dismissal, a follow-up telephone number was obtained and billing forms were completed, and within the next 12-24 hours the subject was contacted by investigator #1 to determine any untoward effects.

Study Procedures and Assessments:

- **Period 1 - screening:**
  - medical/oral history and exam performed, demographics and vital signs (heart rate, blood pressure) obtained, urine pregnancy test as necessary, oral and written informed consent obtained, randomization, lip and tongue palpation rating and training, FAB baseline rating and training.

- **Period 2 - local anesthetic administration**:
  - topical anesthetic applied and allowed to remain in contact with the injection site for 1 minute, wiped clean with dry gauze, one cartridge of 3% mepivacaine administered by investigator #2 or #3 using a standard inferior alveolar block to achieve profound lip numbness. A second injection to be administered at 10 minutes if profound lip numbness not obtained. Oral cavity assessment performed immediately after profound lip numbness obtained.

- **Period 3 - PM/sham administration:**
  - at 25 minutes after last local anesthetic injection oral exam performed, lip numbness confirmed, sensation rating performed, interim FAB (minus drinking water) administered, and vital signs obtained. PM or sham administered at 30 minutes by investigator #2 or #3, employing the same technique used for local anesthetic administration, with patient visual barrier, in a 1:1 ratio with the volume of local anesthetic administered, and completion time recorded.

- **Period 4 - observation period:**
  - soft-tissue anesthesia rating every 5 minutes for 4 hours, oral exam and vital signs every 10 minutes for the first 30 minutes and then every 30

minutes, interim FAB every 5 minutes until interim FAB normal and soft-tissue sensation returned to normal, then final FAB, performed at time when sensation of the lip and tongue returned to normal and the interim FAB finding was normal. If the final FAB was abnormal (inability to drink normally), it was to be repeated every 5 minutes until return to normal on 2 consecutive assessments or end of 4 hour observation period. Any adverse effects during observation period were recorded.

- Period 5 - telephone follow-up:

- within 12-24 hours all subjects contacted by telephone to determine any untoward effects, intraoral pain, and usage of any concomitant medications. For subjects who indicated continuing soft-tissue numbness at 4 hours, the time at which numbness dissipated was also to be obtained.

STATISTICAL ANALYSIS

The primary endpoint used for this study was the efficacy of PM as measured by the time after PM/sham injection to return to normal sensation of the lower lip as evaluated by the standardized palpation technique and defined as the number of minutes elapsed between the injection of PM/sham and the first of two consecutive reports of normal lip sensation. Secondary efficacy endpoints were time to recovery of normal sensation of the tongue as measured by the palpation technique, and time to return to normal oral function as measured by the interim Functional Assessment Battery. The safety and tolerability of PM was evaluated by oral exams, vital sign measurements, and any reports of adverse events. Safety endpoints included the incidence, severity, and duration of adverse effects, including clinically significant findings in the oral cavity and changes in cardiovascular vital signs. We defined any change of greater than 20% from baseline in heart rate and blood pressure readings as a significant deviation, and analyzed for clinical implications.

The p value for comparing age between the two groups was computed using the t test. The p values for comparing binary variables (gender and one or two injections) were computed using Fisher's exact test. Since the time to normal lip sensation and secondary efficacy time end-points do not have a normal distribution, the non-parametric Wilcoxon rank sum test was used to compute p values for the group comparisons. Medians and incidence curves were computed using the Kaplan-Meier method. Descriptive summaries of any positive oral assessment and adverse event findings were reported. All tests were two-sided with a significance level set at $p<0.05$.

RESULTS

Forty-five subjects were enrolled in the study rather than the 44 initially planned, as one of the subjects failed to become profoundly numb after the two prescribed local anesthetic injections and investigation was discontinued before receiving PM/sham injection. This subject was not included in the data analysis. Another subject was determined at data analysis to be a protocol deviation since the PM/sham was injected at 15 minutes instead of 30 minutes after local anesthetic administration. This subject was

also not included in the data analysis. A total of 43 subjects were therefore used in the analysis.

Age and gender were not significantly different between the two groups. The proportion of subjects that necessitated two mepivacaine injections to achieve profound lip anesthesia before receiving PM/sham (4 in the PM group and 2 in the sham group) were not found to be significantly different between the two treatment groups (p=0.4121). Table 1 summarizes these findings by treatment group.

Efficacy:
The median time to recovery of normal sensation of the lower lip after PM/sham injection, our primary efficacy endpoint, was 160 minutes (±13 min) in the sham group and 95 minutes (± 12 min) in the PM group. This was a reduction in duration of numbness of 65 minutes (41%) for the PM group as compared to the sham treatment group (Figure 1), a statistically significant difference (p=0.001) as analyzed by the non-parametric Wilcoxon rank sum test. The percentage of subjects who returned to normal lip sensation within one hour was 24% for the PM group and 5% for the sham group, whereas 27% of sham subjects but none of the PM subjects required more than 3 hours to return to normal lower lip sensation.

The median time to recovery of normal sensation of the tongue after PM injection was 85 minutes (±14 min) in the sham group and 75 minutes (± 13 min) in the PM group. The median time to recovery of oral function, as measured by the FAB was 73 minutes (± 13 min) in the sham group and 50 minutes (± 9 min) in the PM group. The median time to normal speaking was 45 minutes (± 13 min) in the sham group and 50 minutes (± 9 min) in the PM group. The median time to return to a normal smile was 25 minutes (± 13 min) in the sham group and 30 minutes (±9 min) in the PM group. All secondary efficacy endpoints - time to recovery of normal sensation of the tongue and time to recovery of oral function parameters - did not result in statistically significant differences between the PM and sham treatment groups (see Table 2).

Safety:
Oral cavity assessments during the observation period revealed no intraoral sequelae to PM injection other than the expected needle puncture markings.

One subject reported mild transient headache as well as mild intraoral discomfort at the conclusion of the study period, which resolved after taking a standard dose of over-the-counter analgesic at home. One other subject was unable to be contacted for follow-up in spite of multiple attempts at contact. It should be noted that any reported mild tenderness at the injection site for which no analgesic was needed and which resolved before the follow-up phone call was not considered an adverse drug reaction.

Vital sign monitoring revealed both an increase by greater that 20% (5 subjects) and a decrease by greater than 20% (3 subjects) in diastolic blood pressure in subjects who received PM, as well as one subject in the PM group with a decrease in heart rate by

more than 20% from baseline, and one subject in the PM group with an increase in heart rate by more than 20% from baseline. In the sham group of subjects, a deviation greater than 20% from baseline was observed in heart rate (increase in 1 subject, decrease in 1 subject), as well as in systolic blood pressure (increase in 2 subjects, decrease in 1 subject) and diastolic blood pressure (decrease in 3 subjects). All of the volunteers tolerated the changes in vital signs well, without any associated signs or symptoms (Table 3).

DISCUSSION

Efficacy:
As the lip is generally the last soft tissue to recover from local anesthesia, it was chosen as the primary endpoint. This study confirmed that PM significantly reduces the median time to recovery of normal sensation of the lower lip after 3% mepivacaine local anesthesia without vasoconstrictor by 65 minutes (41% reduction in time), which is somewhat comparable to the degree of time reduction achieved by PM administered after local anesthetics containing a vasoconstrictor (4,6,7). In two previous studies evaluating PM after various vasoconstrictor-containing local anesthetic (lidocaine with epinephrine, articaine with epinephrine, prilocaine with epinephrine, or mepivacaine with levonordefrin), Hersh et al (7) reported an 85 minute (55%) reduction in median recovery time of lower lip, while Laviola et al (6) reported a 49 minute (33%) reduction in time to recovery of lower lip sensation. Tavares et al (4) studied the effects of PM following 2% lidocaine with 1:100,000 epinephrine and report a 75 minute (56%) reduction in time to return to normal lip sensation for combined upper and lower lip, and a 120 minute (67%) reduction for lower lip recovery. While these previous studies evaluated PM reversal of local anesthesia with vasoconstrictor, we postulate that PM does not simply antagonize the effects of the vasoconstrictor contained in the local anesthetic cartridge, but rather also enhances the redistribution of local anesthetic away from the site of injection in the pterygomandibular fossa via PM's vasodilatory or other properties, thus speeding the return to a normal sensation in the soft tissues. It appears that the reversal effect may be more profound when vasoconstrictor-containing local anesthetics are used, but the effect when 3% mepivacaine without vasoconstrictor was reversed was also statistically and clinically significant. Although at this time OraVerse® is only FDA approved for reversal of local anesthetics which contain vasoconstrictor, it appears that it is effective with local anesthetics that do not contain vasoconstrictor. This is potentially important in dentistry, particularly in pediatric dentistry where lip injuries are frequent and can be severe, and where 3% mepivacaine is often used as the local anesthetic of choice. Additionally this finding would be important to dentists who treat patients with medical conditions restricting the administration of epinephrine, who now would be able to safely administer PM to reverse the effects of non-vasoconstrictor local anesthetics administered, thereby hastening the return to normal sensation to about 60% of the time it would otherwise require.

This study, however, did not show a similar reduction in median time to recovery of normal sensation of the tongue. This is in contrast to the Laviola et al study, where a statistically significant 31% reduction in time to return of normal tongue sensation was observed, and to the Hersh et al and Tavares et al studies, who report a statistically significant 52% and 60% reduction in tongue recovery times, respectively. However, we noticed that, while overall PM significantly reduced time to recovery in these previous studies, in certain instances in some areas of the mouth the efficacy of PM was minimal or nil – for example, for the maxillary arch, Hersh et al state that "there was an apparent lack of efficacy after the injection of 4% prilocaine with 1:200,000 epinephrine"(7). It is possible that both our study and Hersh's maxillary arch portion of their study do not have enough subjects (power) to detect the clinical effect for the specific local anesthetic and site to be evaluated. Moreover, return of tongue sensation being a secondary end-point, we, as well as other investigators, did not ascertain that the subjects indeed had profound tongue numbness prior to PM administration as we did for lip numbness. Indeed one of our subjects had a profoundly numb lip, but no tongue numbness at all before PM/sham was injected. It is also possible that due to varied individual injection techniques, not enough PM was deposited close to the lingual nerve to produce a favorably significant result. Yet another possibility is that because the local anesthetic did not contain vasoconstrictor, it was not confined to a small area, thus the PM deposited might not have been able to influence redistribution of what was possibly a very small concentration of local anesthetic.

The Functional Assessment Battery (FAB), as developed by Novalar Pharmaceuticals, and previously used to evaluate PM efficacy (7) was utilized to evaluate oral functional impairments because of lingering local anesthetic effect, another secondary efficacy endpoint. Our study did not demonstrate a statistically significantly improved return to baseline FAB after PM injection vs sham, as opposed to Hersh et al who did report a 60 minute (50%) reduction in FAB median time. This discrepancy again might be due to insufficient number of subjects tested. Additionally, although this FAB testing was successfully utilized previously, in our study we found it difficult to objectively gauge normal vs abnormal responses to the speech and smile functions, particularly the smile. In some subjects, even with profound subjective lip numbness, motor function of the lip evaluated by smiling seemed minimally affected. In future studies perhaps other means of assessing oral function would be more objective and reliable; possibly even a simple baseline photograph of the subject's smile could greatly improve the objectivity of this FAB battery of tests.

Safety:
Cardiovascular: Although some changes greater than 20% from baseline were noted with both PM and sham, none of the blood pressure and heart rate values recorded were clinically worrisome, and some of the readings were just minimally outside of the 20% margin. For example, subject #6 whose baseline diastolic BP was 69 mmHg, at 90 min after PM administration had a diastolic reading of 86 mmHg. Although this is more than a 20% change from the baseline value for this subject, a diastolic reading of 86 mmHg certainly would not be considered clinically significant. Moreover we would not expect

that PM, a vasodilator, would have caused a rise in blood pressure, thus it was more likely that other causes led to this increase in blood pressure (such as needing to empty a full bladder). Although we noted many minor deviations from baseline vital signs, none of the values obtained were considered clinically significant, and all of the volunteers tolerated the changes in vital signs well, without any associated signs or symptoms.

Oral Cavity: No changes were observed in the oral cavity following PM administration other than the normal puncture marks for intraoral injection. We consider PM, used in this manner and at the dosages used in our study to be well tolerated intraorally.

FUTURE DIRECTIONS

It is hoped that this small study will lead to future larger scale studies looking at PM and return of normal oral sensation and function with other vasoconstrictor-free local anesthetics. Additionally, studies of PM's reversal efficacy of vasoconstrictor-free local anesthesia of the maxilla, and, perhaps even more importantly, evaluating safety and efficacy of PM for the pediatric dental patient would be of value to all dentists.

CONCLUSIONS

Based on the results of this study, PM significantly reduces the time to recovery of normal sensation of the lower lip following an intraoral inferior alveolar nerve block with 3% mepivacaine local anesthetic without vasoconstrictor by 65 minutes (41%) and is well tolerated, with no clinical adverse effects. PM does not significantly reduce time to return to normal sensation of the tongue following an intraoral inferior alveolar nerve block with 3% mepivacaine local anesthetic without vasoconstrictor, nor hasten return to normal oral function in this study.

Figure 1
Kaplan-Meier curve of: Time to return to normal -- lower lip sensation.

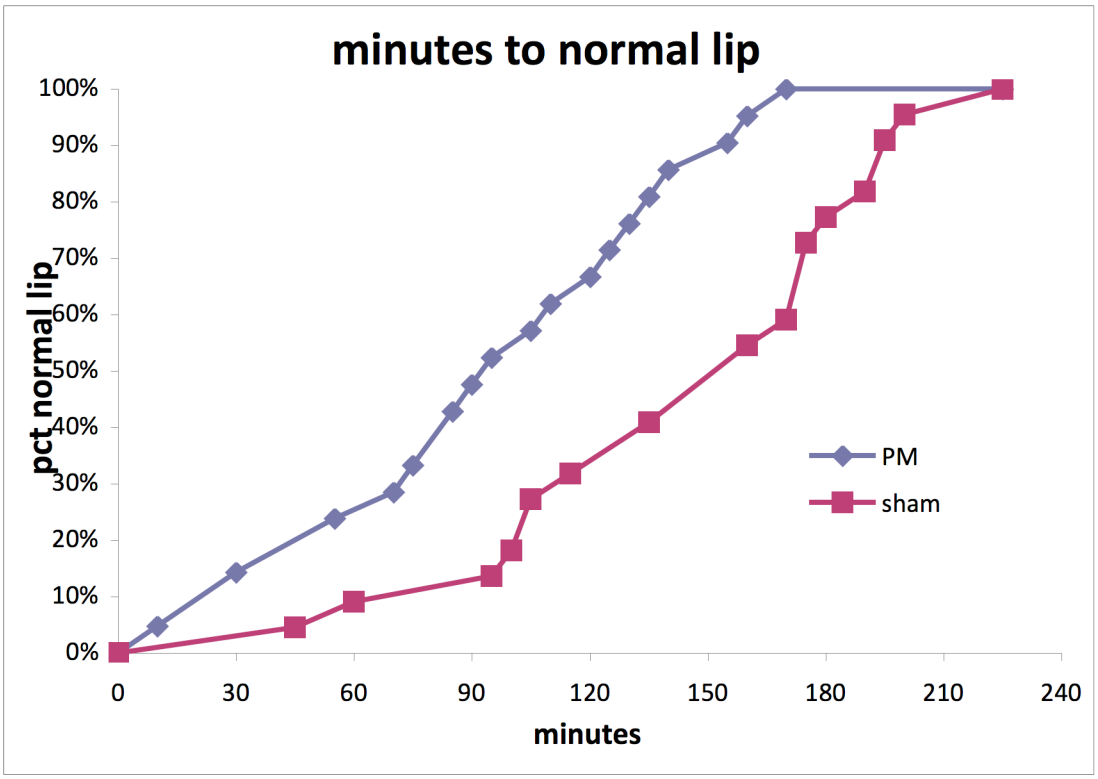

Figure 2
Kaplan-Meier curve of: Time to return to normal -- tongue sensation.

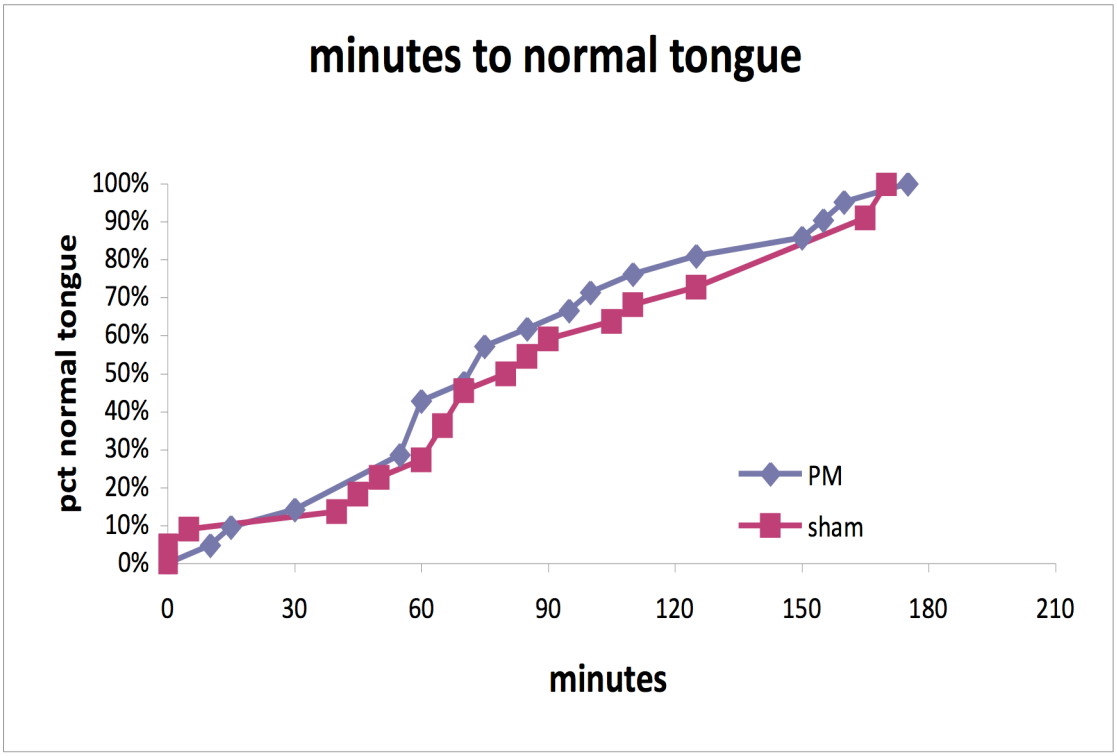

Figure 3
Kaplan-Meier curve of: Time to return to normal -- oral function.

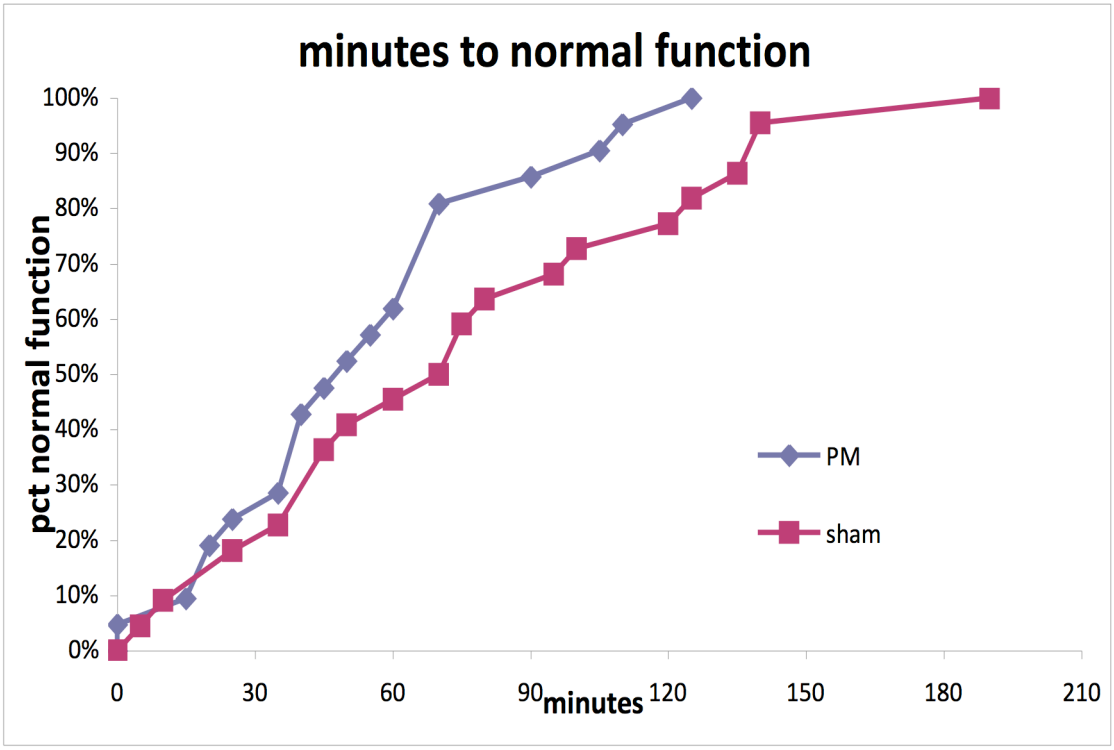

Table 1
Demographics

VARIABLE	PM	SHAM
sex		
male	6	12
female	15	10
total	21	22
age		
mean	36.1 (± 3)	39.2 (± 3)
median	34	31
range	19-65	20-71
two injections	4	2

Table 2
Results – summary

ENDPOINT		median time (±SE median)	time range	p value	Reduction factor
normal lip	PM	95 (± 12)	10 - 170	0.0010	65 min (41%)
	SHAM	160 (± 13)	45 - 225		
normal tongue	PM	75 (± 13)	10 - 175	0.4957	10 min (12%)
	SHAM	85 (± 14)	5 - 170		
normal function	PM	50 (± 9)	0 - 125	0.1222	23 min (32%)
	SHAM	73 (± 13)	5 - 190		
normal reading	PM	50 (± 9)	0 - 120	0.5428	N/A
	SHAM	45 (± 13)	0 - 165		
normal smile	PM	30 (± 9)	0 - 125	0.8624	N/A
	SHAM	25 (± 13)	0 - 190		

Note: -no drooling noted at any observation
-all final FAB findings were normal (no abnormalities noted in any subject in drinking 3 oz. water after interim FAB and all sensation had returned to normal)

Table 3.
Vital Signs – significantly changed from baseline

Subject No - PM/sham	*time*	*BP*	*BP >20%*	*HR*	*HR >20%*
3 - PM	baseline	127/76		74	
	at 30 min.	138/95	Diastolic-high	72	
6 - PM	baseline	125/69		66	
	at 90 min.	131/86	Diastolic-high	57	
7 - PM	baseline	139/57		91	
	at 10 min.	132/90	Diastolic-high	76	
	at 60 min.	144/91	Diastolic-high	76	
	at 90 min.	134/80	Diastolic-high	72	
10 - sham	baseline	135/83		68	
	at 30 min.	141/88		89	HR-high
14 - sham	baseline	101/66		82	
	before PM	125/72	Systolic-high	90	
	at 90 min.	124/71	Systolic-high	87	
	at 150 min.	126/76	Systolic-high	90	
16 - sham	baseline	151/90		88	
	before PM	160/91		61	HR-low
	at 20 min.	166/86		66	HR-low
20 - PM	baseline	128/58		58	
	at 60 min.	117/49		46	HR-low
	at 90 min.	116/56		46	HR-low
21 - sham	baseline	102/66		55	
	before PM	88/47	Diastolic-low	55	
	at 120 min.	113/84	Diastolic-high	51	
24 - sham	baseline	122/77		68	
	at 20 min.	120/58	Diastolic-low	69	
26 - PM	baseline	104/54		66	
	before PM	102/70	Diastolic-high	60	
	at 10 min.	114/65	Diastolic-high	59	
	at 20 min.	106/69	Diastolic-high	63	
	at 30 min.	103/66	Diastolic-high	57	
27 - PM	baseline	106/64		83	
	at 10 min.	101/47	Diastolic-low	77	
31 - sham	baseline	129/79		62	
	at 20 min.	137/98	Diastolic-high	60	
34 - PM	baseline	119/51		78	
	before PM	121/64	Diastolic-high	66	
	at 10 min.	120/78	Diastolic-high	61	HR-low
	at 20 min.	130/70	Diastolic-high	70	

	at 30 min.	127/67	Diastolic-high	60	
	at 60 min.	129/70	Diastolic-high	65	
	at 90 min.	128/70	Diastolic-high	59	HR-low
	at 120 min.	127/67	Diastolic-high	68	
35 - sham	baseline	131/71		78	
	at 10 min.	128/48	Diastolic-low	78	
	at 90 min.	129/98	Diastolic-high	75	
36 - sham	baseline	102/65		64	
	before PM	136/71	Systolic-high	70	
	at 20 min.	123/56	Systolic-high	66	
	at 60 min.	123/76	Systolic-high	64	
38 - PM	baseline	117/64		69	
	before PM	107/64		88	HR-high
	at 150 min.	138/39	Diastolic-low	71	
39 - sham	baseline	150/78		80	
	at 90 min.	147/95	Diastolic-high	92	
41 - sham	baseline	136/73		58	
	at 20 min.	137/91	Diastolic-high	59	
	at 60 min.	134/99	Diastolic-high	62	
42 - sham	baseline	122/89		62	
	at 20 min.	128/54	Systolic-low	60	
43 - PM	baseline	143/92		83	
	at 10 min.	130/68	Diastolic-low	84	
44 - PM	baseline	138/88		70	
	at 10 min.	165/52	Diastolic-low	68	

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