RANDOMIZED CONTROL TRIAL

Phase Four, Randomized, Double-Blinded, Controlled Trial of Phentolamine Mesylate in Two- to Five-year-old Dental Patients

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Abstract: ***Purpose:*** *The purpose of this study was to evaluate, using a randomized, double-blind methodology: (1) the safety of phentolamine mesylate (Oraverse) in accelerating the recovery of soft tissue anesthesia following the injection of two percent lidocaine plus 1:100,000 epinephrine in two- to five-year-olds; and (2) efficacy in four- to five-year-olds only.* ***Methods:*** *One hundred fifty pediatric dental patients underwent routine dental restorative procedures with two percent lidocaine plus 1:100,000 epinephrine with doses based on body weight. Phentolamine mesylate or a sham injection (two to one ratio) was then administered. Subjects were monitored for safety and, in four- to five-year-olds, for efficacy during the two-hour evaluation period.* ***Results:*** *There were no significant differences in adverse events between the phentolamine and sham injections. Compared to sham, phentolamine was not associated with nerve injury, increased analgesic use, or abnormalities of the oral cavity. Phentolamine was associated with transient decreased blood pressure in some children. In four- and five-year-olds, phentolamine induced more rapid recovery of lip anesthesia by 48 minutes ($P<0.0001$).* ***Conclusions:*** *Phentolamine was well tolerated and safe in three- to five-year-olds; in four- to five-year-olds, a statistically significant more rapid recovery of lip sensation compared to sham injections was determined.* *(Pediatr Dent 2017;39(1):39-45) Received May 7, 2016 | Last Revision October 17, 2016 | Accepted October 19, 2016*

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Providing pain control by administering local anesthetic agents containing a vasoconstrictor (epinephrine or levonordefrin) is a routine part of outpatient dentistry.[1] One of the shortcomings of dental local anesthetic agents, especially when employed for routine restorative and scaling procedures that are usually completed in an hour or less, is that the duration of soft tissue anesthesia (numbness to the lip and tongue) typically lasts for three to five hours.[2] These types of dental procedures produce significantly less ($P<0.05$) postprocedural pain than stainless steel crowns and pulpotomies,[3] although 25 to 30 percent of children report pain following restorative dentistry procedures.[3,4] Approximately 15 percent of children also complain about numbness after dental treatment.[3] The persistent anesthesia beyond the procedure is also associated with difficulty in eating, drinking, speaking, drooling, and inadvertent biting of the lips, tongue, and cheek.

The results of a prospective study of 320 children showed that 16 percent of four- to seven-year-olds and 13 percent of eight- to 11-year-olds reported having postoperative soft tissue trauma after mandibular block injections that profoundly numbed the lower lips and tongue.[5] The swelling and tissue injury associated with this type of trauma has even led to at least one reported hospital emergency room visit and the unnecessary administration of antibiotic therapy, because the tissue appearance resembled that of a postprocedural infection.[6]

Phentolamine mesylate is a nonselective alpha-adrenergic blocking agent that has been in the United States marketplace since 1952. It lacks intrinsic activity but possesses higher affinity than norepinephrine and epinephrine for postsynaptic alpha-adrenergic receptors; thus, it antagonizes (reverses) their vasoconstrictive action. It was originally developed to treat hypertension.[7]

An intraoral submucosal injectable formulation of phentolamine mesylate was developed by Novalar Pharmaceuticals (San Diego, Calif., USA) to help terminate the numbing action of local anesthesia when it is no longer desired. This product contains 0.4 mg phentolamine mesylate packaged in a 1.7-mL dental cartridge. Based on the results of two phase two and two phase three randomized placebo- or sham-controlled clinical trials (see Table 1 for description of FDA clinical trial phases),[7-9] phentolamine mesylate, under the proprietary name OraVerse (Septodont Inc., Lancaster, Pa., USA) was granted FDA approval in 2008 for accelerating the return of sensation and function following nonsurgical dental procedures requiring local anesthetic plus epinephrine or levonordefrin in adult and pediatric dental patients as young as six years old.[10]

The first published placebo-controlled phase two study reported that, in 10- to 58-year-old dental patients, an injection of phentolamine, at a one-to-one volume ratio at the site of the previous local anesthetic injection, accelerated median

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Table 1. DESCRIPTION OF FDA CLINICAL TRIAL PHASES

Phase 1	A small group (10-30) of normal volunteers, usually without the disease condition, is evaluated to assess dose, pharmacokinetics, and safety.
Phase 2	A larger group of subjects with the disease condition (in this case, those with lip and tongue numbness after local anesthetic injections) are evaluated. This involves efficacy, establishing a dose-response, safety, and pharmacokinetic studies. Up to a few hundred individuals are typically studied.
Phase 3	An even larger group of patients with the disease condition are studied. Efficacy and safety are again evaluated; dosing schedules are firmly established. Five hundred to 1,000 subjects are typically evaluated. After the completion of Phase 3, the pharmaceutical manufacturer submits a new drug application to the FDA. The FDA may approve, deny approval, or request that additional research be performed on the drug.
Phase 4	This occurs following FDA drug approval. Additional studies may be performed to support marketing claims or broaden the label (in this case, that phentolamine mesylate is effective and safe in children younger than six years old). Another part of Phase 4 is post-marketing drug surveillance. As the drug is used by or administered to many thousands of patients, rare side effects that were not seen in Phase 1 to 3 clinical trials may become apparent to clinicians and reported to the FDA through the Medwatch System. This may result in additional side effects being added to the drug's package insert or even removal of the drug from the market.

recovery time to normal sensation of the upper and lower lips by 55 percent or 85 minutes.[8] There was no difference in the incidence or severity of adverse events between the phentolamine and the placebo vehicle group.

Two large pivotal phase three studies employed a sham injection instead of a placebo injection because the FDA advised that the injection of a placebo vehicle added unnecessary risk. In these two studies, the median recovery time to normal lip sensation was accelerated by 55 percent or 85 minutes in the mandibular arch ($P<0.0001$) and 62 percent or 82.5 minutes in the maxillary arch ($P<0.0001$) compared to sham injections.[7] Likewise in the mandibular arch, the median time to recovery of normal sensation of the tongue was accelerated by 52 percent or 65 minutes in the tongue ($P<0.0001$). Median times to return of normal function (ability to smile, speak normally, and drink three ounces of water) were accelerated by 52 percent and 43 percent in the mandibular and maxillary arches, respectively ($P<0.0001$). Subjects were not able to discriminate what was described as faint pain between the actual phentolamine injection and the sham injection.

Because phentolamine is an alpha-adrenergic blocking agent, there was a particular interest in any possible changes in cardiovascular function, most notably hypotension and/or reflex tachycardia after the phentolamine injections. There were no differences in measures of sitting or standing systolic blood pressure, diastolic blood pressure, or heart rate at any time point compared to the sham injection (most likely due to the fact that the amount of phentolamine employed for local anesthetic reversal is six- to 12-fold less than that employed to reduce blood pressure).

An additional pivotal phase two clinical trial was performed in 152 four- to 11-year-old dental patients (96 in the phentolamine group and 56 in the sham group) who received two percent lidocaine plus 1:100,000 epinephrine prior to the initiation of routine dental restorative or periodontal maintenance procedures.[8] While the primary goal of this study was to access safety, 115 of the children who were at least six years old were able to complete efficacy assessments of the lips and the tongue. Two of the 96 subjects (2.1 percent) in the phentolamine group and one of the 56 subjects (1.8 percent) in the sham group had a transient fall in systolic or diastolic blood pressure of more than 20 mm. Similar to the adult studies, phentolamine accelerated recovery of normal lip sensation; combined mean acceleration in the mandibular and maxillary arches was by 56 percent or 75 minutes ($P<0.0001$).[8] These children were also not able to discriminate any pain experienced from the phentolamine injections versus the sham injections based on their responses to the Wong-Baker Faces Pain-Rating Scale (**W-B PRS**).[11,12]

Since the release of phentolamine in dentistry, several additional clinical trials have been published confirming these initial findings.[13-15] A recent meta-analysis has reviewed the literature and found seven eligible clinical trials that validate the efficacy of phentolamine for soft-tissue reversal of anesthesia and its overall safety.[16]

As with other alpha-adrenergic-blocking agents, phentolamine's primary effect is vasodilatation. Following the administration of local anesthetic with vasoconstrictor, a subsequent phentolamine injection into the same location enhances the redistribution of the local anesthetic away from the injection site,[17] explaining the more rapid return of normal intraoral and perioral sensation.

At the time of the present study, the dental formulation of phentolamine mesylate was only approved in patients six years of age and older. Data providing clear evidence of safety and efficacy in younger children were needed by both the FDA and pediatric dentists.

The purpose of this phase four, multicenter, randomized, double-blind controlled clinical trial was to evaluate the safety and tolerability of the soft tissue anesthetic reversal agent phentolamine when administered to two- to five-year-olds. For four- to five-year-olds, a secondary objective was to assess the efficacy of soft tissue anesthesia reversal.

Methods

The study was carried out at seven dental centers: University of Washington, Seattle, Wash., USA; Nationwide Children's Hospital, Columbus, Ohio, USA; Indiana University School of Dentistry, Indianapolis, Ind., USA; University of Pennsylvania School of Dental Medicine, Philadelphia, Pa., USA; University of California School of Dentistry, San Francisco, Calif., USA; Jean Brown Research Center, Salt Lake City, Utah, USA; and the University of Pittsburgh School of Dental Medicine, Pittsburgh, Pa., USA. Each of the seven centers acquired Institutional Review Board approval to carry out the study, and at least one parent or guardian signed an informed consent document. The data collection occurred between February 2012 and August 2014.

The eligibility criteria for participation included: male or female patients two to five years old who were sufficiently healthy, as determined by the site investigator to receive routine dental care. Patients requiring a restorative procedure in a single quadrant of the mouth—requiring local anesthesia with lidocaine two percent with 1:100,000 epinephrine administered by submucosal injection (inferior alveolar blocks for the mandible) that could be completed in 60 minutes—were included in this study. Four- and five-year-olds needed to be capable of being trained to assess lip sensation.

Exclusion criteria included patients who: had a weight less than 10 kg (weight less than 15 kg if four or five years old); had a history or presence of any condition that contraindicates routine dental care or use of local anesthetic; required more than one fourth of a cartridge of local anesthetic if their weight was equal to or greater than 10 kg and less than 15 kg, more than one half of a cartridge of local anesthetic if their weight was equal to or greater than 15 kg and less than 30 kg, or more than one cartridge of local anesthetic if their weight was equal to or greater than 30 kg (excluding supplemental injections to achieve anesthesia of the teeth); allergy or intolerance to lidocaine, epinephrine, sulfites, phentolamine, nitrous oxide, or topical benzocaine; had used any investigational drug and/or participated in any clinical study within 30 days of study drug administration; participated in this study or any previous study of phentolamine mesylate for reversal of local soft tissue anesthesia; used commercial phentolamine within 30 days of study drug administration; and used opioid or opioid-like analgesics within 24 hours prior to administration of local anesthetic.

There were six study periods. All procedures were research-related unless otherwise indicated as standard of care.

Table 2. DEMOGRAPHICS AND BASELINE DATA OF STUDY POPULATION

Treatment groups	Phentolamine	Sham control
Subjects n (%)	99 (100)	51 (100)
Female	46 (46.5)	23 (45.1)
Male	53 (53.5)	28 (54.9)
Weight kg±SD	19.9±3.9	20.2±5.1
Age Mean ys±SD	4.2±0.8	4.1±0.9
2 (n)	2	3
3 (n)	18	8
4 (n)	39	20
5 (n)	40	20
Anesthetic injection arch n (%)		
Mandibular	48 (48.5)	23 (45.1)
Maxillary	51 (51.5)	28 (54.9)
Dose (1.7 ml cartridges)		
¼ cartridges	5 subjects	6 subjects
½ cartridges	91 subjects	42 subjects
1 cartridge	3 subjects	3 subjects
Baseline cardiovascular parameters Mean mm Hg beats/min†*		
Systolic blood pressure*	95.0±9.8	96.0±9.5
Diastolic blood pressure*	59.4±6.5	59.9±8.5
Heart rate†	93.1±12.3	91.8±12.9

Period one—screening (up to two weeks prior to or on day one). A research coordinator or an investigator explained the study and the informed consent to a parent or legal guardian of the child. After the parent read the informed consent document and all questions had been answered, they signed the informed consent with a research coordinator or investigator as the witness. Medical history was recorded by interviewing the parent, and dental history was recorded via the respective institution's dental chart. Demographics were recorded, including height, weight, and sex of the child. The research coordinator then trained four- and five year-old subjects in the use of W-B PRS.[11,12] At certain key points in the study, including immediately after the local anesthetic injection and immediately after the phentolamine or sham injection, the children were asked to rate any pain they experienced using this scale. The Pediatric Functional Assessment Battery (**pFAB**) asked subjects to give a big smile, pronounce 10 words, and drink one ounce of water; an investigator or coordinator would then look for the presence of drooling. A lip/tongue palpation procedure (where the child is asked to tap their lip and, in the case of mandibular injections, also their tongue on the side to be anesthetized and compare it to the side that will not be anesthetized) was also employed. Training on assessments of safety and efficacy occurred on day one. Two- to three-year-olds were only evaluated for safety.

Period two—anesthetic administration and dental procedure (day one). Prior to anesthetic administration a general oral cavity assessment was performed, where the oral cavity was examined for any sites of hyperemia, ulceration, or edema. If indicated, an investigator administered topical anesthetic (benzocaine) to the injection site and nitrous oxide/oxygen sedation by mask (30 to 50 percent nitrous oxide balanced with oxygen). Subsequently, an investigator unblinded to the phentolamine or sham treatment administered two percent lidocaine with 1:100,000 epinephrine (one quarter, one half, or one cartridge, depending on the child's weight) to anesthetize the target tooth/teeth. Immediately after the injection, the child rated the injection pain employing W-B PRS. An oral cavity assessment was then performed around the injection site. An unblinded investigator performed the restorative dental procedure(s) in one quadrant of the mouth.

Period three—study drug administration (day one). Following the completion of the restorative procedure, the research coordinator confirmed for four- to five-year-olds that the subjects had at least one abnormal pFAB test (smiling, speaking, drinking, drooling) and/or numbness to the lip by having the child employ palpation techniques. An interactive telephone voice response system was employed to assign specific closed kits containing a phentolamine or sham cartridge (at a two-to-one ratio) containing a unique identification number. The unblinded investigator picked up the study kit and placed a visual barrier on the subject. All other study-related personnel left the research room. With a visual barrier in place, the unblinded investigator administered phentolamine (at a volume equal to the local anesthetic) or the sham injection at the same site as the previous lidocaine with epinephrine injection. The plastic shield remained on the needle for the sham injection, and no drug was delivered (it was simply pushed against the oral mucosal tissues where an injection would have been delivered). The unblinded investigator then placed the phentolamine or sham cartridges back in the kit, placed the needle shield back on the active phentolamine syringe so that all syringes appeared

identical, and closed the kit. The unblinded investigator's role in the study was then complete. A blinded investigator or blinded research coordinator then administered the W-B PRS so that the child could rate the phentolamine or sham injection from one to five (no pain to hurts worst). The blinded investigator or blinded research coordinator then administered the pFAB, in which the child was asked to smile, pronounce 10 words, and drink an ounce of water, and the presence of any drooling was noted. The child then rated their lip and, in the case of mandibular injections, tongue numbness as normal, tingling, or numb, employing lip and tongue palpation procedures. Blood pressure and pulse were then recorded by the research coordinator as well as any adverse events.

Period four—observation period (day one). The observation period for all subjects was two hours. Two- to five-year-olds were assessed for safety (blood pressure, pulse, and any spontaneously observed adverse events). W-B PRS assessments, pFAB, and lip/tongue palpation procedures were performed in four- to five-year-olds every 15 minutes for two hours. A telephone follow-up was scheduled that evening with the parent, and the subject accompanied by their parent was then discharged.

Period five—telephone follow-up (evening of day one). Telephone follow-ups for adverse events were performed by the research coordinator using nonsuggestive questions such as: "How is your child doing? and "Is he smiling, speaking, eating, and drinking normally?" The parent was also asked about any concomitant medications, including analgesics (acetaminophen or ibuprofen) that the child had taken for mouth pain.

Period six—in-clinic safety follow-up (day two or three). The parent and child returned to the pediatric dental clinic one or two days after study drug administration. The parent was queried about any additional adverse events, intraoral pain, and concomitant medications ingested. In addition, a general and site-specific oral exam was performed. This completed the child's participation in the study.

Statistical analysis. The primary objective of this study was the safety and tolerability of phentolamine (Oraverse) in two- to five-year-olds undergoing mandibular or maxillary dental restorative procedures with local anesthesia provided by two percent lidocaine with 1:100,000 epinephrine. The safety and tolerability of phentolamine were evaluated based on the incidence of adverse events, clinically significant changes in vital signs, clinically significant changes in oral cavity assessments, any clinical indication of nerve injury, and the use of postprocedural analgesics by the child. Tabulations of adverse events by severity grade and casual relationship to study drug were provided. The duration and outcome of each adverse event were reported. Of special interest was a comparison of the W-B PRS severity scores immediately after the injection of phentolamine or sham.

The study was not powered to detect treatment differences in secondary efficacy endpoints, and efficacy assessments were only performed on four- and five-year-olds (who were trainable). The time to return to normal function, as measured on the pFAB, was summarized descriptively by treatment group using the Kaplan-Meier method. The estimated median time to recovery for each group and their corresponding 95 percent confidence interval were reported. The stratified log-rank test was used to test the null hypothesis that the distributions for the time to recovery between the two treatment groups were different. The aforementioned methods were also employed to summarize differences in the time to return of normal lip and tongue sensation.

Results

Demographics and disposition. This pediatric clinical trial enrolled 99 subjects into the phentolamine treatment group and 51 subjects into the sham group. As shown in Table 2, the background and other baseline characteristics were similar across the treatment groups and procedure locations; treatment groups were well balanced for gender, age, weight, and mouth arch. Two-year-olds were difficult to recruit and only five were enrolled in the entire study; thus firm safety conclusions in this age strata could not be made. Topical anesthetics were used on nearly all subjects (98 percent), and nitrous oxide was used for approximately 80 percent of subjects in both the phentolamine and sham injection treatment groups. The majority of subjects (91.9 percent) in the phentolamine treatment group received one half cartridge of phentolamine. A slightly higher proportion of subjects (59.6 percent) in the phentolamine group reported prior or current medical conditions. Asthma was the most commonly reported medical condition in both the phentolamine group (19.2 percent) and sham injection group (11.8 percent); after asthma, skin problems were the most commonly reported medical condition in both groups (7.1 percent and 9.8 percent, respectively). Both treatment groups received the assigned study drug in an average of approximately 29 minutes after being administered local anesthetic.

Safety. A total of 48 of the 150 subjects reported 58 adverse events, and no subject discontinued participation due to an adverse event. All but one adverse event was rated as mild or moderate in intensity. A single severe adverse event of intraoral pain was experienced by a subject randomized to the sham injection.

For the majority of the adverse events (**AEs**) that were deemed related to study drug treatments (30 total), a slightly higher proportion of phentolamine subjects reported treatment-related AEs (19.2 percent) versus the sham subjects (15.7 percent; Chi .596, ns). Oral pain was reported in the

Table 3. INCIDENCES OF CHANGES IN CARDIOVASCULAR VITAL SIGNS*

Treatment groups	Phentolamine n (%)	Sham control n (%)
Total	**99 (100)**	**51 (100)**
Systolic blood pressure criteria[1]		
>20 mm Hg decrease	12 (12.1)	3 (5.9)
Diastolic blood pressure criteria[2]		
>20 mm Hg decrease	7 (7.1)	1 (2)
Pulse criteria[3]		
>20 bpm increase	10 (10.1)	3 (5.9)
Meets one of more of the above criteria	24 (24.2)	7 (13.7)*

* Chi-square=2.27. *P*=0.131, nonsignificant. The criteria for significant changes in vital signs were pre-established and included: decrease in systolic blood pressure (supine or sitting) of >20 mm Hg on two consecutive measurements after the administration of study drug relative to the baseline systolic blood pressure; decrease in diastolic blood pressure (supine or sitting) of >20 mm Hg on two consecutive measurements after the administration of study drug relative to the baseline diastolic blood pressure; and increase in pulse (supine or sitting) of 20 bpm on two consecutive measurements after the administration of study drug relative to the baseline pulse.

Table 4. ANALYSIS OF RECOVERY TIMES IN SUBJECTS WHO COMPLETED EFFICACY ASSESSMENTS

Treatment groups	Phentolamine	Sham control
Median time to normal lip sensation	61.0 mins	109.0 mins
(95% confidence interval)	45.0-62.0 mins	91.0-123.0 mins
Reduction of in time until recovery	48 mins	
Treatment population	N=71	N=37
P-value for log-rank test	<0.0001	
Median time to normal tongue sensation	60.0 mins	91.0 mins
95% confidence interval	45.0-76.0 mins	44.0-NA mins*
Reduction in time to recovery	31 mins	
Treatment population	N=36	N=17
P-value for log-rank test	0.5719	
Median time to normal function-pFAB†	31.0 mins	45.0 mins
95% confidence interval	30.0-42.0 mins	31.0-63.0 mins
Reduction in time to recovery	18 mins	
Treatment population	N=56	N=29
P-value for log-rank test	0.0559	

* NA=upper limit of confidence interval could not be determined.

† pFAB=Pediatric Functional Assessment Battery.

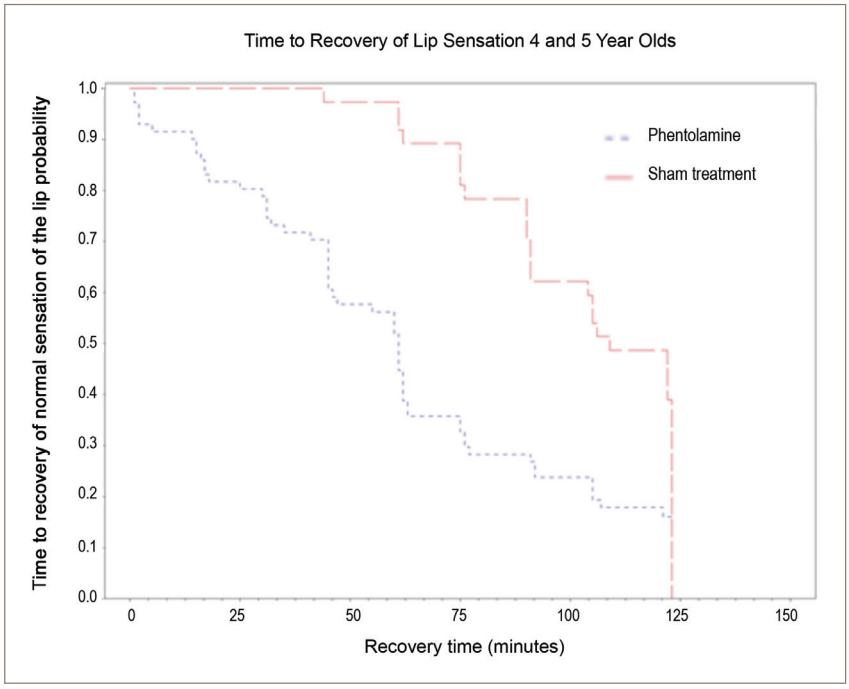

Figure. Time to return of normal lip sensation employing a standardized finger palpation procedure. Recovery curves for phentolamine and sham are Kaplan Meier time-to-event analysis plots. Phentolamine significantly (*P*<0.0001) accelerated the return of normal lip sensation compared to sham over the two-hour observation period. Phentolamine treatment is plotted in blue dots, and sham treatment is plotted in red dashes.

phentolamine group with a higher frequency (10.1 percent) than the sham group (3.9 percent), but these results were not statistically significant (chi 0.186, ns). Other AEs that were reported at a low frequency but at equal to or greater than two percent included, for phentolamine and sham respectively: hypoesthesia (zero percent and 3.9 percent); aphthous stomatitis (zero percent and two percent); mouth discoloration (zero percent and two percent); mouth swelling (zero percent and two percent); mouth injury (zero percent and two percent); and toothache (two percent and zero percent).

Clinically significant changes in the vital signs were observed in both treatment groups (Table 3). When compared to pretreatment, the phentolamine group had a higher frequency of subjects (12 subjects, 12.1 percent) displaying a decrease of greater than 20 mm Hg in systolic blood pressure relative to measurements of prior to study drug; three subjects or 5.9 percent of subjects displayed this clinically significant change in systolic blood pressure in the sham group. A slightly higher proportion of subjects in the phentolamine treatment group (seven subjects, 7.1 percent) also displayed a decrease of greater than 20 mmHg in diastolic blood pressure relative to measurements prior to study drug; relative to this baseline, only one subject (two percent) in the sham group displayed this change. Lastly, an increase in heart rate of greater than 20 bpm was observed in 10 phentolamine subjects (10.1 percent) and three sham subjects (5.9 percent). Overall, in assessing the number of subjects experiencing one of more of the clinically significant changes in cardiovascular vital signs mentioned above, the proportion of subjects in the phentolamine group had a higher incidence of subjects (24 subjects, 24.2 percent) in comparison to the sham group (seven subjects, 13.7 percent; chi-square equals 2.27, *P*=0.131 NS) with one or more clinically significant changes in vitals.

Overall, the incidence of subjects in both treatment groups experiencing intraoral pain (as measured by the W-B PRS) is comparable at all time points post study drug administration, including immediately after study drug administration. The mean W-B PRS scores for the sham group continuously decreased over time, but peaked in the phentolamine group (0.8) after study drug administration before decreasing in a comparable fashion to the sham group. The phentolamine group had three subjects (3.8 percent) reporting the most severe pain (hurts worst); in comparison, the sham group had no such reports. However, the observation is likely not indicative of the study drug, since the sample proportion of subjects in the phentolamine group reported this pain severity prior to study drug administration. Thus, the duration and severity of intraoral pain measured by the W-B PRS was comparable between the two treatment groups.

Results of the oral cavity assessments, both a broad evaluation of the mouth and specific to procedure and injection site, showed minor abnormalities. The proportion of subjects in each treatment group with clinically significant abnormalities were similar across all time points.

Lastly, there were no reports of nerve injury (paresthesia) in both treatment groups, and the frequency of subjects with analgesic use during

the two-hour observation period and within 48 hours of discharge was higher in the sham group. This data reveal that treatment with phentolamine is not associated with an increased use of analgesics for intraoral pain or nerve injury.

Efficacy. Trainable four- and five-year-old subjects who were able to provide efficacy data were included in the analysis to determine whether phentolamine accelerates the time to normal function and sensation, as measured by the pFAB and standardized lip and tongue sensation ratings (Table 4). The median time to normal function in the phentolamine group was 31 minutes and 45 minutes in the sham group. Phentolamine reduced the median time to normal function by 14 minutes, but based on the stratified log-rank test, this difference was not statistically significant (P=0.0559). The median time to return of normal lip sensation of the combined maxillary and mandibular data sets was 61 minutes in the phentolamine group and 109 minutes in the sham group (Figure). Phentolamine significantly reduced the median time to normal lip sensation by 41 minutes (P<0.0001). A subgroup analysis of 36 phentolamine subjects and 21 sham subjects also confirmed that phentolamine significantly reduced the median time to mandibular lip sensation by 54.5 minutes over the sham group (stratified log rank, P=0.0074). A similar subgroup analysis of 35 subjects in the phentolamine group and 16 subjects in the sham group revealed that phentolamine also significantly reduced the median time to normal lip sensation for subjects undergoing maxillary procedures by 58.5 minutes (stratified log rank, P=0.0009).

Time to recovery of normal tongue sensation was analyzed in a group of 36 phentolamine subjects (36.4 percent) and 17 sham subjects (33.3 percent). The median time to normal tongue sensation was 60 minutes in the phentolamine group and 91 minutes in the sham group. Phentolamine reduced the median time to normal tongue sensation by 31 minutes, but this was not statistically significant (P=0.5719). Phentolamine was also able to accelerate the time to normal function, but the results did not quite reach statistical significance (P=0.0559).

Discussion

Phentolamine mesylate (Oraverse) has been FDA-approved in children as young as six years old for approximately nine years. The results of this study indicate that the drug can be safely employed in children as young as three years old. Since only five two-year-olds were enrolled in the study and only two of them received an active drug (Table 2), definitive conclusions in this age group could not be made. In regards to efficacy, a statistically and clinically significant acceleration in the return of normal lip sensation for phentolamine compared to sham injections was demonstrated in four- to five-year-olds. Unlike studies previously published in adults and children as young as six years old,[7-9] statistically significant accelerations in the return of function were not observed. This is possibly due to difficulty of the four- and five-year-olds in the present study interpreting these endpoints or because the sample size was simply underpowered.

One of the possible weaknesses of this sham-controlled study was children being able to discern when a needle with the accompanying phentolamine injection pierced their mucosa and expanded their tissues versus a sham injection when these events did not occur. However, based on the W-B PRS, this did not appear to occur. In addition, the FDA felt that exposing these young children to vehicle placebo injections, added unnecessary risk to the study.

The results also revealed that phentolamine is associated with a statistically insignificant increase in the incidence of oral pain compared to sham (10.1 percent versus 3.9 percent respectively). Phentolamine's alpha adrenergic blocking activity, leading to shorter anesthetic times, is probably the reason behind this finding. While also not statistically significant, transient reductions in blood pressure and increases in pulse rate occurred in some children. Systemic vasodilation by phentolamine can lower blood pressure with an accompanying reflex tachycardia.

The holy grail study in young children would be to address if the administration of phentolamine actually reduced the incidence of lip and tongue mutilation after local anesthetic injection. If one assumes a 10 percent incidence of this phenomenon, a study like this would have to enroll close to 1,000 subjects to demonstrate statistical significance of phentolamine over a sham injection. However, largely based on the results of the current study, the FDA recently approved the use of phentolamine mesylate (Oraverse) in children as young as three years old.

Conclusions

Based on this study's results, the following conclusions can be made:

1. Phentolamine mesylate appears safe in three- to five-year-old pediatric dental patients.
2. Phentolamine mesylate significantly accelerated the return of lip sensation in four- and five-year-olds who received two percent lidocaine plus 1:100,000 epinephrine for restorative dental procedures.
3. It is still unknown whether the ability of phentolamine to accelerate the return of lip sensation translates into a reduction of local anesthetic-induced soft tissue injury in this very young dental population.

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References

1. Moore PA, Hersh EV. Local anesthetics: pharmacology and toxicity. Dent Clin North Am 2010;54(4):587-99.
2. Hersh, EV, Hermann DG, Lamp CJ, Johnson PD, MacAfee KA. Assessing the duration of mandibular soft tissue anesthesia. J Am Dent Assoc 1995;126(11):1531-6.
3. Staman NM, Townsend JA, Hagan JL. Observational study: discomfort following dental procedures for children. Pediatr Dent 2013;35(1):52-4.
4. Acs G, Drazner E. The incidence of postoperative pain and analgesic usage in children. J Dent Child 1992;59 (1):48-52.
5. College C, Feigal R, Wandera A, Strange M. Bilateral versus unilateral mandibular block anesthesia in a pediatric population. Pediatr Dent 2000;22(6):453-7.
6. Hersh E, Lindemeyer R. Phentolamine mesylate for accelerating recovery from lip and tongue anesthesia. Dent Clin North Am 2010;54(4):631-42.
7. Hersh EV, Moore PA, Papas AS, et al. Reversal of soft-tissue local anesthesia with phentolamine mesylate in adolescents and adults. J Am Dent Assoc 2008;139(8): 1080-93.
8. Laviola M, McGavin SK, Freer GA, et al. Randomized study of phentolamine mesylate for reversal of local anesthesia. J Dent Res 2008;87(7):635-9.
9. Tavares M, Goodson JM, Studen-Pavlovich D, et al. Reversal of soft-tissue local anesthesia with phentolamine mesylate in pediatric patients. J Am Dent Assoc 2008; 139:1095-104.
10. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. OraVerse. Available at: "http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Addlsearch_drug_name". Accessed January 25, 2017.
11. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988;14(1):9-17.
12. Wong DL, Baker CM. Smiling faces as anchor for pain intensity scales. Pain 2001;89(2-3):295-300.
13. Fowler S, Nusstein J, Drum M, Reader A, Beck M, Fowler S. Reversal of soft-tissue anesthesia in asymptomatic endodontic patients: a preliminary, prospective, randomized, single-blind study. J Endod 2011;37(10):1353-8.
14. Nourbakhsh N, Shirani F, Babaei M. Effect of phentolamine mesylate on duration of soft tissue local anesthesia in children. J Res Pharm Pract 2012;1(2):55-9.
15. Elmore S, Nusstein J, Drum M, Reader A, Beck M, Fowler S. Reversal of pulpal and soft tissue anesthesia using phentolamine: a prospective randomized, single-blind study. J Endod 2013;39(4):429-34.
16. Prados-Frutos JC, Rojo R, González-Serrano J, González-Serrano C et al. Phentolamine mesylate to reverse oral soft-tissue local anesthesia: a systematic review and meta-analysis. J Am Dent Assoc 2015;146(10):751-9.e3.
17. Moore PA, Hersh EV, Papas AS, et al. Pharmacokinetics of lidocaine with epinephrine following local anesthesia reversal with phentolamine mesylate. Anesth Prog 2008; 55:40-8.