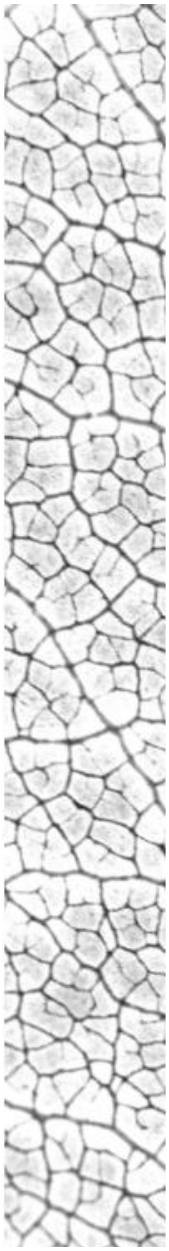

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Unaddressed local anesthesia reversal action of phentolamine mesylate after plain mepivacaine

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Abstract

Background and Aim: Clinical studies concerning the effect of intraoral injection of phentolamine mesylate on the duration of soft tissue anesthesia and its related functional deficits after using a plain local anesthetic are scarce. This study is to evaluate the efficacy and safety of phentolamine mesylate as a local anesthesia reversal agent after plain mepivacaine using mental/incisive nerve block. **Methods:** Twenty patients who received plain mepivacaine as a local anesthetic were randomly assigned into two groups: group I (sham injection group) and group II (phentolamine mesylate group). Sham injection or phentolamine mesylate injection was given 30 minutes after mepivavaine injection. Time to return to normal soft tissue sensation and normal oral functions was recorded to assess efficacy of phentolamine mesylate. Intraoral assessment, monitoring hemodynamic vital signs and presence of any drug-related adverse effects were used to assess safety of phentolamine mesylate. **Results:** there were statistically significant differences ($p< 0.001$) in the mean duration to recovery of normal sensation in the lower lip, chin and gums between group I and group II. Also there were statistically significant differences ($P<0.001$) in the mean duration to perceive normal sensation and in the mean duration to demonstrate normal oral functions between the two groups. No statistically significant differences were observed in hemodynamic vital signs between periods of measurements in each group nor between the two groups. No changes were observed on intraoral examination and no drug related adverse events occurred. All patients were satisfied with the rapid recovery of normal sensation and oral functions.
Conclusion: Phentolamine mesylate is efficient and safe for rapid recovery of normal sensation and oral functions after using plain mepivacaine

Keywords: local anesthesia, phentolamine mesylate, vasoconstrictors, soft tissue anesthesia, oral functional deficits, mental/incisive nerve block

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INTRODUCTION

Vasoconstrictors are added to most dental local anesthetics to increase their effectiveness and prolong the duration of anesthesia (Katagiri et al. 2020) but due to the fact that mepivacaine causes milder vasodilation than other local anesthetics so it causes profound anesthesia with longest duration of action when used as a plain anesthetic compared with other local anesthetic agents when used without vasoconstrictors (Bortoluzzi et al.2018). There is no significant difference in the duration of soft tissue anesthesia caused by plain 3% mepivacaine and 2% lidocaine with 1:100,000 epinephrine (Hersh et al. 1995) Plain mepivacaine is recommended whenever a vasoconstrictor is contraindicated and is commonly used by dentists to treat geriatric and pediatric patients (Malamed 2019).

The average length of a dental appointment is 44 minute. Anesthesia of the bone and soft tissues usually lasts for several hours after loss of pulpal anesthesia. Extended time of soft tissue anesthesia impairs patients' normal daily activities in three aspects: perceptual (perception of altered physical appearance), sensory (loss of sensation), and functional (altered ability to speak, smile, eat, drink, and control drooling (Grover et al. 2015) Long lasting soft tissue anesthesia can be detrimental, inconvenient, and unnecessary (Eldor and Nguyen 2018). This is especially important in pediatric and geriatric patients where prolonged numbness could be injurious (Srikar et al. 2015).

Phentolamine mesylate is a non-selective antagonist of alpha adrenergic receptors which was approved by the U.S. Food and Drug Administration (FDA) to reverse soft tissue anesthesia and associated functional deficits that result from the injection of dental local anesthetics containing a vasoconstrictor (Devadiga

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Table 1. The sequences used in this study. Abbreviations for deposited collection as follows: NK-Nia Kurniawan (Universitas Brawijaya, Indonesia); PT-Panupong Thammacoti (Chulalongkorn University, Thailand); AM-Anita Malbotra (Bangor University, United Kingdom); UMMZ-Museum Zoology, University of Michigan (United States)

No	Specimen Number	Taxon	Country	Accession Number	Locality	Source
1	Isolate K1	*C. rhodostoma*	Indonesia	MT722041	Kangean, East Java, Indonesia	This study
2	Isolate K3	*C. rhodostoma*	Indonesia	MT722043	Kangean, East Java, Indonesia	This study
3	Isolate K23	*C. rhodostoma*	Indonesia	MT722059	Kangean, East Java, Indonesia	This study
4	Isolate K2	*C. rhodostoma*	Indonesia	MT722042	Sapanjang (Kangean) East Java, Indonesia	This study
5	Isolate K5	*C. rhodostoma*	Indonesia	MT722044	Sapanjang (Kangean) East Java, Indonesia	This study
6	Isolate K9	*C. rhodostoma*	Indonesia	MT722047	Trenggalek, East Java, Indonesia	This study
7	Isolate K20	*C. rhodostoma*	Indonesia	MT722057	Majalengka, West Java, Indonesia	This study
8	Isolate K21	*C. rhodostoma*	Indonesia	MT722058	Majalengka, West Java, Indonesia	This study
9	NK 1270	*C. rhodostoma*	Indonesia	MT722045	Cilacap, Central Java, Indonesia	This study
10	NK 1271	*C. rhodostoma*	Indonesia	MT722046	Cilacap, Central Java, Indonesia	This study
11	Isolate K28	*C. rhodostoma*	Indonesia	MT722060	Cilacap, Central Java, Indonesia	This study
12	NK 1607	*C. rhodostoma*	Indonesia	MT722048	Ketapang, West Borneo, Indonesia	This study
13	NK 1608	*C. rhodostoma*	Indonesia	MT722049	Ketapang, West Borneo, Indonesia	This study
14	NK 1609	*C. rhodostoma*	Indonesia	MT722050	Ketapang, West Borneo, Indonesia	This study
15	NK 1610	*C. rhodostoma*	Indonesia	MT722051	Ketapang, West Borneo, Indonesia	This study
16	NK 1611	*C. rhodostoma*	Indonesia	MT72252	Ketapang, West Borneo, Indonesia	This study
17	NK 1612	*C. rhodostoma*	Indonesia	MT722053	Ketapang, West Borneo, Indonesia	This study
18	NK 1613	*C. rhodostoma*	Indonesia	MT722054	Ketapang, West Borneo, Indonesia	This study
19	NK 1614	*C. rhodostoma*	Indonesia	MT722055	Ketapang, West Borneo, Indonesia	This study
20	PT 297	*C. rhodostoma*	Thailand	MT722056	Nakon Si Thammarat, South Thailand	This study
21	UMMZ 184314	*C. rhodostoma*	Thailand	U41878	Thailand	Kraus and Brown 1998
22	Isolate RS-S	*Hypnale nepa*	Malaysia	KC347491	Sri Lanka	Pyron et al. 2013
23	Isolate RAP0552	*Hypnale zara*	India	KC347513	India	Pyron et al. 2013
24	Isolate A53-	*Hypnale hypnale*	India	AY352812	India	Malhotra and Thorpe 2004
25	AM B306	*Ovophis chaseni*	Malaysia	AY352825	Mt. Kinabalu, Sabah, Malaysia	Malhotra and Thorpe 2004

et al. 2019). Because it acts as a vasodilator, this allows faster dissipation of the LA into the vasculature. When the LA diffuses into the cardiovascular system away from the injection site, less of the LA will be available to block sodium channels, thus diminishing anesthesia which in turn accelerates return of normal sensation (Fowler, 2010) Phentolamine mesylate causes vasodilation by blocking the effect of endogenously released catecholamines in the oral tissues of cats (Koss, 2002). The blockade of the action of the endogenously released norepinephrine and the resultant increase in the blood flow may be the actual mechanism by which phentolamine mesylate can reverse the action of plain local anesthetics (Goswami et al. 2014). Since there is no studies evaluating the efficacy and safety of phentolamine mesylate for reversal of soft tissue anesthesia and the related functional deficits after using plain local anesthetics, this study aim to evaluate the safety and ability of phentolamine mesylate to reduce the duration for recovery of soft tissue sensation and normal oral functions after mental/incisive nerve block with 3% mepivacaine hydrochloride.

MATERIAL AND METHODS

Sample Collection

The tissue sample used was obtained from Java, Karimun Java, Kangean, Borneo Island, with addition to the Thailand population (**Table 1**). The dorsal muscle tissue was preserved in 95% ethanol in a small tube, and preserved specimens from the Indonesia population were deposited in the Laboratory of Ecology and Animal Biodiversity, Department of Biology, Brawijaya University.

Samples used for the evaluation of storage conditions in its influence in PLA_2 activity were taken from the Java population. A total of 6 snake individuals were maintained in an individual cage and were fed routinely. Venom milking was conducted after fasting, pooled together, and aliquoted into a smaller volume to be stored at the various condition. We performed three levels of storage time: 7, 9, and 14 days; and temperature: 37°C, 4ºC, and -80ºC.

Genetic Relationship Analysis

The DNA extraction procedure was performed by Qiagen (QIAamp DNA Mini Kit) company protocol with slight modification. Muscle tissue was crushed and dissolved in ATL Buffer, followed by vortex for 15 sec. The sample was incubated for 1–3 h at 56ºC. The homogenized sample was then added by 200 µl of AL buffer, followed by incubation at 70ºC for 10 min, and added by 200 µl of absolute ethanol. The whole solution was transferred into the QIAamp mini spin column, added by washing buffer AW1 and centrifuged at 8000 rpm (1 min). Pellet in the spin column was added by washing buffer AW2 and centrifuged at 14000 rpm (1 min). DNA precipitation in the spin column membrane was added by Elution buffer and was incubated at 15–25ºC for 1 min, followed by centrifugation at 8000 rpm for 1 min. DNA can be found in the supernatant part.

Amplification of collected DNA was performed by using ND4 forward primer F: 5’ CAC CTA TGA CTA CCA AAA GCT CAT GTA GAA GC 3’; and Leu reverse primer R: 5’ CAT TAC TTT TAC TTG GAA TTT GCA CCA 3’

(Arévalo 1994, Wostl et al. 2016). The amplification cycle comprises early denaturation (hot-start) which was performed at 94ºC (3 min), 30 times of denaturation at 94ºC (30 sec), annealing at 52ºC (45 sec), elongation at 72ºC (60 sec), and late elongation at 72ºC (7 min). Amplified results were qualitatively assayed through 2% gel electrophoresis and sequenced (FirstBase, Malaysia). The DNA sequences were contig and edited by sequencer 4.1.4 (Gene Codes, Ann Arbor, Michigan, USA) and ChromasPro 1.34 (Tomohiko Shimada, Kyoto University, Japan), and evaluated by eye for the quality. The sequences were deposited on GenBank (GenBank Accession No: MT722041-MT722060, **Table 1**).

As much as ~650 bp of alignment sequence were used for phylogenetic analysis and genetic distances. The similarity among DNA sequences and data in GenBank were analyzed through BLAST. Sequence alignment was conducted using MEGA7 (Kumar et al. 2016). The uncorrected p-distance values were grouped based on the locality of the sample. the ingroup including all of the *C. rhodostoma* from Indonesia and Thailand population, *Ovophis chaseni*, and *Hypnale* spp. are chosen as the outgroup (**Table 1**). The phylogenetic tree was reconstructed by Bayesian Inference model. The best evolution model was determined by Kakusan4 (Tanabe 2011). Bayesian inference was analyzed in MrBayes 3.04b (Huelsenbeck and Ronquist, 2001) using 5 million generations for the chain lengths of MCMC. The estimation was sampled every 1000 multiple generations with a topology consensus of 25%. The reconstruction result was considered valid as if the Bayesian posterior probability (BPP) reaches 0.95 or more (Huelsenbeck and Ronquist, 2001). and -80ºC.

Venom Storage Condition Analysis

The concentration of venom protein was measured as a prior step of the whole analysis series. 1 µl sample solution from each storage condition was measured the absorbance in the presence of 280 nm light wavelength through the NanoDrop instrument. The absorbance value was equalized into the protein content unit per solution sample volume (mg ml^{-1}). The data was used as the basis for further assays.

The crude venom solution that had been measured for the protein concentration was then dissolved by sterile equates and followed to be processed under reducing condition (Reducing Sample Buffer 1:1 v/v). The solution of the sample and RSB was heated at 100ºC for 15 min. A total of 23 µg protein content inside a 10 µg sample solution was then conducted into SDS-PAGE, with 3% and 15% gel concentration for stacking and separating gel respectively. Electrophoresis was performed in a constant voltage of 120 V. Jena Bioscience BlueEye Prestained Marker 10-245 kDa was used as a standard marker to measure the molecular weight of the separated protein sample. The CBB staining process was conducted to visualize the sample protein separation results.

The svPLA2 activity of *C. rhodostoma* was assayed by the acidimetric method based on Tan and Tan (1988). One part of egg yolk was mixed with 1 part of 18 mM $CaCl_2$ and 1 part of 8.1 mM sodium deoxycholate. The phospholipid substrate solution formed was mixed well and adjusted by 1 M NaOH to reach a pH of 8.0. The sample solution with a concentration of 50 µg/100 µl was poured into a 15 ml substrate solution. The pH was measured by meter using QIS Netherland Make Portable Meter in a 5–65 sec period, where the decrease of 1 pH unit was equal to the release of 133 µmol fatty acids as the products of phospholipids hydrolysis.

The statistical analysis was performed by SPSS 20.0. Normal and homogenous variant data were ANOVA tested, followed by univariate analysis and Tukey test.

RESULTS

The most important outcomes to be considered in our study concerning the efficacy of PM as a local anesthesia reversal agent is the reduction in the time needed to return to normal sensation (loss of numbness and tingling). Subjects in group I reported a mean duration of lip anesthesia of 74.00± 20.11 minutes while group II reported a mean duration of lip anesthesia of 19.00± 7.37 minutes. This was a statistically significant difference ($p< 0.001$). The mean duration of chin anesthesia was 73.00± 24.06 minutes in group I, while it was 21.00± 7.37 minutes in group II. This was a statistically significant difference ($p<0.001$). The mean duration of gum anesthesia was 53.00± 21.62 minutes in group I, while it was 15.00± 5.27 minutes in group II. This was a statistically significant difference ($p<0.001$) (**Table 2**). The reduction in the time needed for recovery to normal sensation in group II was accompanied by similar reduction in both the times at which patients perceived their complete recovery and the times at which there was a demonstration of complete recovery of functions as assessed by the STAR-7 questionnaire and the FAB assessment, respectively. Subjects in group I reported a mean duration to perceive recovery to normal sensation of 84.00± 27.56 minutes while subjects in group II reported a mean duration to perceive recovery to normal sensation of 30.00± 00 minutes. This was a statistically significant difference ($p<0.001$). In group I, a mean time of 55.50± 23.74 minutes was needed to demonstrate normal functions while in group II a mean time of 18.50± 3.374 minutes was needed to demonstrate normal functions. This was a statistically significant difference ($p<0.001$) (**Table 3**).

Table 2. Comparison of the mean differences of the duration of anesthesia in the lower lip, chin and gum between group I and group II

Study variables	Group	N	Mean	SD	t-test	P-value
Lip	Group I	10	74.00	20.11	8.11	<0.001*
	Group II	10	19.00	7.37		
Chin	Group I	10	73.00	24.06	6.53	<0.001*
	Group II	10	21.00	7.37		
Gum	Group I	10	53.00	21.62	5.39	<0.001*
	Group II	10	15.00	5.27		

P≤ 0.05 was considered as significant

Table 3. Comparison of the mean differences of time(minutes) needed to return to normal study variables between group I and group II

Study variables	Group	N	Mean	SD	t-test	P-value
Star	Group I	10	84.00	27.56	6.19	<0.001*
	Group II	10	30.00	0.00		
FAB	Group I	10	55.50	23.74	4.87	<0.001*
	Group II	10	18.50	3.374		
Objective smile	Group I	10	55.50	23.74	4.87	<0.001*
	Group II	10	18.50	3.37		
Subjective smile	Group I	10	42.00	21.49	4.38	<0.001*
	Group II	10	12.00	2.58		

P≤ 0.05 was considered as significant

Table 4. The mean differences in the hemodynamic changes between two periods of measurements in group I and group II

Study Group	Study variables	N	Mean	SD	Paired t-test	P-value
Group I	SBP Pre-drug	10	113.90	13.44	-0.995	0.346
	SBP 10minutes post-drug	10	116.00	14.95		
	DBP pre-drug	10	75.80	11.79	0.789	0.45
	DBP 10 minutes post-drug	10	77.10	10.27		
	HR pre-drug	10	78.00	13.05	0.164	0.873
	HR10 minutes post-drug	10	77.80	10.93		
	SaO_2 pre-drug	10	97.70	1.88	-1.809	0.104
	SaO_2 10 minutes post-drug	10	98.10	1.72		
Group II	SBP Pre-drug	10	120.10	16.55	2.149	0.06
	SBP 10minutes post-drug	10	115.00	13.49		
	DBP pre-drug	10	81.10	7.96	1.909	0.089
	DBP 10 minutes post-drug	10	79.00	9.71		
	HR pre-drug	10	82.50	4.30	-0.215	0.834
	HR10 minutes post-drug	10	82.70	6.09		
	SaO_2 pre-drug	10	98.90	0.31	-1.000	0.343
	SaO_2 10 minutes post-drug	10	99.00	0.00		

P≤0.05 was considered as significant

Table 5. Comparison of the mean differences of hemodynamic changes between group I and group II

Study variables	Group	N	Mean	SD	t-test	P-value
SBP 10minutes post-drug	Group I	10	116.00	14.95	0.157	0.877
	Group II	10	115.00	13.49		
DBP 10 minutes post-drug	Group I	10	77.10	10.27	-0.425	0.676
	Group II	10	79.00	9.71		
HR10 minutes post-drug	Group I	10	77.80	10.93	-1.238	0.236
	Group II	10	82.70	6.09		
SaO2 10 minutes post-drug	Group I	10	98.10	1.72	-1.646	0.134
	Group II	10	99.00	0.00		

Non-significant changes in hemodynamic vital signs were observed between the two times of measurements within each of the two groups (**Table 3**) and between group I and group II 10 minutes after sham / phentolamine mesylate injections (**Table 4**).

No pain was reported by any subject in group I while a mean of pain level of 14.4 mm according to Heft-Parker visual analog scale was reported by subjects in group II 90 minutes after phentolamine mesylate injection. No drug-related adverse effects occurred in either groups. No changes were seen on intraoral examination.

DISCUSSION

Phentolamine mesylate is a nonselective α-adrenergic blocker, is the first pharmacological agent used for reversing soft-tissue anesthesia and the associated functional deficits that result from the injection of LA containing a vasoconstrictor (Yagiela, 2011; McDonald et al. 2016) Previous pharmacokinetic studies supposed a mechanism of action of phentolamine mesylate based on antagonism of the vasoconstrictor added to the local anesthetics which would result in increased absorption of the local anesthetic to the systemic circulation(Hersh et al.2008;

Moore et al. 2008) Various studies have evaluated the efficacy and safety of phentolamine mesylate reversal of local anesthetics that contain vasoconstrictors (Saunders et al.2011; Boynes et al.2011; Babaei et al. 2012). Studies on phentolamine mesylate as a local anesthesia reversal agent after vasoconstrictor-free local anesthetics are inadequate. In our study we hypothesized that phentolamine mesylate hastens the reversal of the local anesthesia by the faster dissipation of the local anesthetic solution itself from the site of injection by the vasodilatory effect of phentolamine mesylate that results from the blockade of the action of the endogenously released norepinephrine rather than from antagonizing the effect of the added vasoconstrictors.

In group II, there was significant decrease in the mean duration needed to return to normal sensation (in the lower lip, chin and gum) compared with group I (Table). The reduction in the mean duration to recovery of normal sensation of the lower lip is consistent with Silvera, (2013) who found that 3% mepivacaine reduces the mean duration to return to normal sensation of the lower lip by 65 minutes. In this study there were a correlating significant reduction in the median duration to return to normal oral functions (as measured by FAB) in group II (who received PM after plain mepivacaine) compared with group I (**Table 2**), such significant reduction does not coincide with Silvera, (2013) who did not find such a significant reduction. The reduction in the sensation and oral functions parameters in group II may be due to the fact that PM can block the effect of endogenously released norepinephrine and enhance local blood flow causing rapid dissipation of the local anesthetic (Goswami et al. 2014) Non-significant statistical differences on comparison of the vital signs between two periods of measurements within each group of the study (**Table 3**) nor between the two groups 10 minutes after sham/phentolamine mesylate injection (**Table 4**). The absence of significant changes in the hemodynamic vital signs may be due to the low dose of intraorally injected phentolamine mesylate (0.4 mg) which is approximately six- to twelve-fold less than the intramuscular or intravenous doses used in medicine (Hersh et al. 2008).

The safety results demonstrated that injections of 0.4 mg PM in group II was well tolerated by subjects. Pain ratings at the injection site were increased 90 minutes after PM administration. The mean level of pain ratings was in the area of faint pain according to HP VAS which has no clinical significance and it resolved spontaneously within 24 hours. These results coincide with (Fowler et al., Daubländer et al. 2017; Helmi et al.2018) . This pain may be due to the rapid reversal of anesthesia causing fast unmasking of the pain caused by dental treatment (Laviola et al. 2008) or may be due to the intrinsic effect of PM (Babaei et al. 2012).

CONCLUSION

Within the limitations of the present study, it can be concluded that after mental/incisive nerve block with 1.8 ml of 3% mepivacaine hydrochloride, phentolamine mesylate is safe and effective in the reversal of soft tissue anesthesia and its associated functional deficits.

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