The effect of eutectic mixture of local anesthesia (EMLA) cream on sympathetic response and radial artery spasm during transradial coronary angiogram

Young Jin Youn

The Graduate School, Yonsei University
Department of Medicine

The effect of eutectic mixture of local anesthesia (EMLA) cream on sympathetic response and radial artery spasm during transradial coronary angiogram

A Masters thesis
Submitted to the Department of Medicine
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Master of Medical Science

Young Jin Youn

July 2010 of submission

This certifies that the masters thesis
of Young Jin Youn is approved.

_____
Thesis Supervisor: [Junghan Yoon]

_____
[Jang-Young Kim]

_____
[Hyun Kyo Lim]

The Graduate School

Yonsei University

July 2010

감사의 글

먼저 본 논문이 완성되기까지 세심한 지도와 격려로 이끌어 주시고 많은 가르침과 할 수 있다는 자신감을 주신 윤정한 교수님께 감사 드립니다. 교수님의 지도로 논문을 하나하나 완성해 가면서 제 자신이 커가는 것을 느꼈고, 교수님의 애정 어린 질책으로 인해 논문의 틀이 마련될 때마다 즐거움을 느꼈습니다.

그리고 실제적으로 논문과 데이터를 관리하는 실제적인 모든 것을 가르쳐 주신 김장영 교수님과 애정을 가지고 논문 내용을 세심히 검토해 주신 임현교 교수님께 진심으로 감사 드립니다. 연구 과정에서 조언을 해주신 최경훈, 유병수, 이승환 교수님께도 감사 드립니다.

마지막으로, 말없이 항상 저를 믿어주고 용기를 북돋아준 아내 희원과 항상 웃음을 주는 성원, 성준이에게 감사의 마음을 전합니다.

2010년 7월

저자 씀

Contents

LIST OF FIGURES

LIST OF TABLES

Abstract

The effect of eutectic mixture of local anesthesia (EMLA) cream on sympathetic response and radial artery spasm during transradial coronary angiogram

Background and Objectives: Radial artery spasm (RAS) is one of the most common complications of the transradial angiography (TRA). Radial artery is prone to cathecholamine-induced contraction and the radial pain during procedure could increase the level of sympathetic response (SR). We evaluated the effect of eutectic mixture of local anesthesia (EMLA) cream on SR and RAS during TRA.

Methods: Total 76 patients underwent TRA were enrolled. All patients were randomized to EMLA or control group according to the use of EMLA cream on wrist before TRA. Wrist pain was evaluated by the visual analogue scale (VAS) and verbal rating scale (VRS-4) during lidocaine infiltration and introducer sheath insertion. SR parameters including systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were measured at baseline, after lidocaine infiltration, after puncture and after sheath insertion.

RAS was determined by the pre-defined clinical findings and angiographic finding.

Results: The baseline characteristics were not different between two groups. The wrist pain was lower in EMLA group during lidocaine infiltration (VAS: 3.1 ± 1.7 vs. 4.0 ± 1.7, $p = 0.04$; VRS-4: 2.0 ± 0.5 vs. 2.2 ± 0.5, $p = 0.03$, respectively). The SR was significantly blunted in EMLA group than placebo group from baseline to lidocaine infiltration (ΔSBP, mmHg: 5 ± 10 vs. 13 ± 12, $p < 0.01$; ΔDBP, mmHg: 2 ± 8 vs. 7 ± 12, $p = 0.03$; ΔMAP, mmHg: 3 ± 8 vs. 9 ± 10, $p < 0.01$; ΔPR, beat/min: 2 ± 4 vs. 8 ± 14, $p < 0.01$; ΔSV, ml: 3 ± 6 vs. 21 ± 17, $p < 0.01$; ΔCO, l/min: 0.2 ± 4.8 vs. 1.5 ± 1.4 $p < 0.01$ ΔTPR, mmHg·l/min; 1.0 ± 3.2 vs. 5.9 ± 8.2, $p < 0.01$, respectively). Although clinical or angiographic RAS was not different, minimal luminal diameter at the start of procedure was significantly larger in EMLA group (1.78 ± 0.54 mm vs. 1.51 ± 0.41 mm, $p = 0.02$).

Conclusion: The EMLA cream could reduce the wrist pain and SR during lidocaine infiltration. In addition, benefit of EMLA cream on RAS at the start of the procedure is expected by larger minimal luminal diameter.

Key words: Anesthesia, local; Coronary angiography; Radial artery

The effect of eutectic mixture of local anesthesia (EMLA) cream on sympathetic response and radial artery spasm during transradial coronary angiogram

Young Jin Youn

Department of Medicine

The Graduate School Yonsei University

(Directed by Professor Junghan Yoon)

1. Introduction

The use of transradial coronary angiography (TRA) and intervention are increasing due to lower major vascular access related complications and the potential for early mobilization.[1,2] Radial artery spasm (RAS) is one of the most common complications of the TRA and related to patient's discomfort and lower procedural success rate.[3,4] The rate of RAS varies from 12% in patients with a contraindication to femoral approach to 22% in patients receiving no intra-arterial vasodilators.[5,6]

The radial artery has a predominance of α adrenoceptors and is therefore prone to catecholamine-induced contraction.[7] Ruiz-Salmerón et al have reported that moderate-to-severe pain during radial artery cannulation was associated with RAS.[8]

A eutectic mixture of local anesthetic cream (EMLA®; Laboratorie ASTRA, Manterre, France), composed of lidocaine 2.5% and prilocaine 2.5%, is known to be an effective topical anesthetic agent. It is used for a variety of painful cutaneous procedures on intact skin, including phlebotomy, intravenous catheterization, arterial cannulation and lumbar puncture. Kim et al reported that EMLA cream can effectively reduce the wrist pain during TRA without any significant drug-related complications when the application time is 1 to 3 hours before the procedure.[9]

The aim of this study was to test the hypothesis that the EMLA cream can reduce the sympathetic response by reducing the radial pain and this can lead to reduce the RAS during TRA.

2. Materials and methods

2. 1 Study subjects

A total of 76 subjects who were need of coronary angiography were enrolled in this study from September 2008 to March 2009. All subjects were randomly assigned to EMLA group or control group according to the use of EMLA cream on wrist before TRA by a simple randomization table. Coronary angiography was performed after insertion of 5-Fr. introducer sheath at either side of radial artery. All subjects signed informed consent forms for participation in this study.

2.2 Method

2.2.1 Application of study cream

We provided blinded tubes containing either EMLA cream or placebo which was an odorless white cream that resembled the EMLA cream. All EMLA and placebo creams were applied to both wrists 1 cm above the styloid process of the radius and then covered with a transparent 5 cm dressing (Fig. 1). The amount of EMLA or placebo cream used was 2.5 gm, the standard adult dose. The EMLA or placebo cream was applied on the wrist from 1 to 3 hours before the procedure. The subjects and the physician performing the coronary angiography were blinded as to which cream was applied.

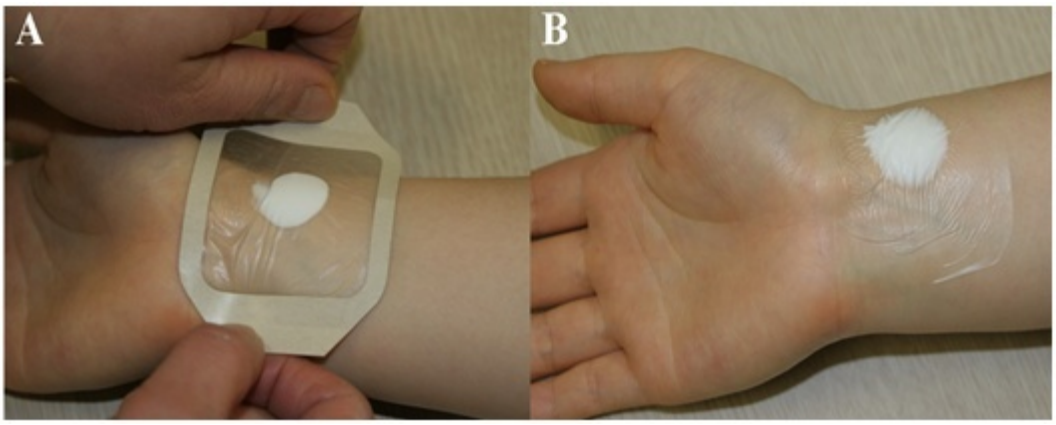

Figure 1. Application of study cream for transradial coronary angiography
The vascular access site was pasted with the EMLA or placebo cream (A) and sealed with a transparent cover (B).

2.2.2 Performing radial artery cannulation and coronary angiography

A loading dose of 600 mg clopidogrel and 300 mg aspirin was given to all subjects at least three hours before the procedure. The radial artery was punctured using a 20-G venous needle (Sindonbang Company, Korea) at a point 5 - 10 mm proximal to the styloid process after the subcutaneous infiltration with 0.6 ml of 2% lidocaine. A 5 Fr. introducer sheath (Terumo Company, Japan) was inserted into the radial artery. After sheath insertion, 5000 IU of heparin was administered into radial artery via introducer sheath. All subjects underwent coronary angiography with a 4 to 5-Fr. catheter. The shape and size of the catheters was selected by the operator's discretion.

2.2.3 Estimating the radial pain

Each subject was asked to identify the pain score during lidocaine infiltration and introducer sheath insertion. The pain score was assessed by a visual analogue scale (VAS) and a 4-category verbal rating scale (VRS-4).[10] On the VAS, the subjects indicated their pain intensity by making a mark on a 10-cm long line that included descriptors labeled at each end of the line of pain intensity (*e.g.*, from "no pain" to "pain as bad as it could be"). The subject was instructed to regard the VAS as a continuum and to make a mark at the point along the line corresponding to his/her current level of pain. The score was determined by measuring the distance from the left end of the line to the subject's mark. Scoring of VRS-4 consists of a finite list of intensity descriptors: 1 point = "no pain"; 2 points = "a little pain"; 3 points = "painful, but tolerable"; 4 points = "most pain possible".

2.2.4 Measurement of the sympathetic response parameters

As parameters of sympathetic tone, systolic (SBP) and diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse rate (PR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were measured continuously and non-invasively by

using finger photoplethysmography (Finometer; Finapres Medical Systems. Netherlands). Previous studies showed that Finometer recordings accurately reflect sympathetic response.[10-13]

The finger cuff was applied to the midphalanx of the middle finger on opposite hand of vascular access site. To avoid hydrostatic level differences, the hand was continuously positioned at right atrial level in the mid-axillary line. After applying the Finometer, the subject was stabilized for 5 – 10 minutes. We used the mean values of sympathetic tone for 1 minute before lidocaine infiltration as the values of baseline. In the pilot phase of our study, we observed that the sympathetic response began to increase 5 - 30 seconds after noxious stimulus and decrease immediately after peak and the time to peak was different among the parameters (Fig. 2). So, we used the peak value of SBP, DBP, MAP, PR, SV, CO and TPR during 30 - 40 second after lidocaine infiltration, after puncture and after introducer sheath insertion. Sympathetic response was estimated by calculating the absolute difference between values of baseline and values after lidocaine infiltration, between values after lidocaine infiltration and values after puncture and between values after puncture and values after introducer sheath insertion.

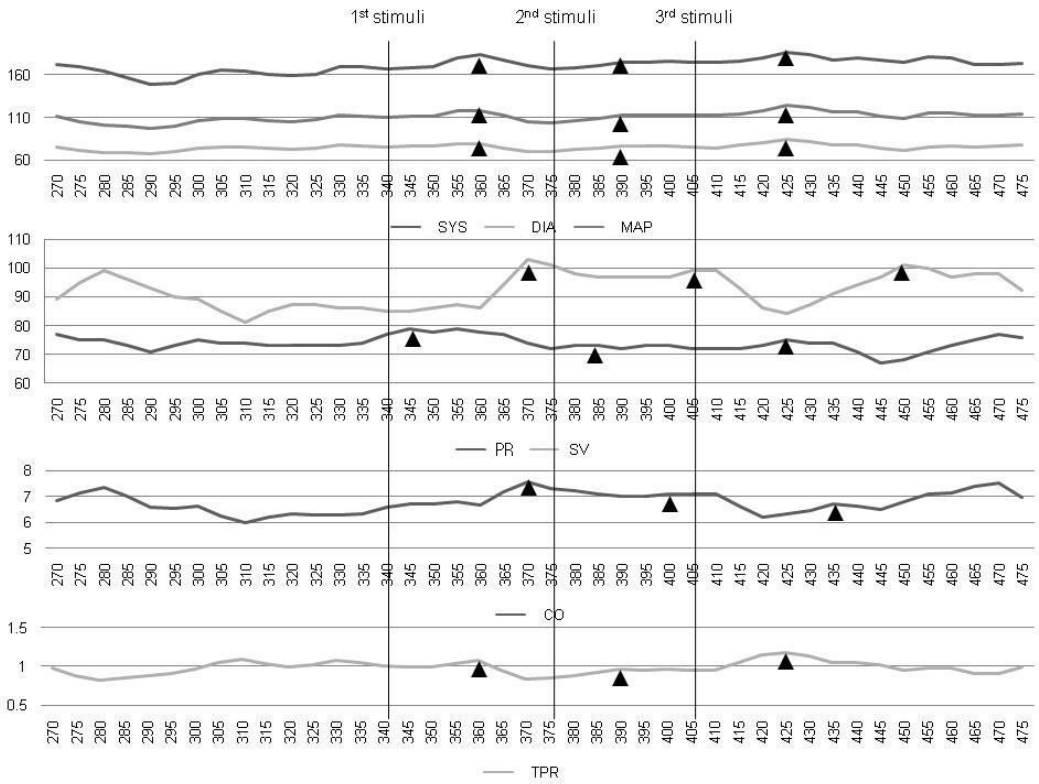

Figure 2. Example recording of sympathetic response parameters

Sympathetic tone begins to increase 5 -30 seconds after each noxious stimulus and begins to decreases immediately after peak. The time to peak is different among the parameters. Triangle marks indicate the peak value of each parameter after noxious stimuli. Y axis: unit of each parameter; X axis: time (second). SYS, systolic blood pressure (mmHg); DIA, diastolic blood pressure (mmHg); MAP, mean arterial pressure (mmHg); PR, pulse rate (beat/min); SV, stroke volume (ml); CO, cardiac output (l/min); TPR, total peripheral resistance (mmHg·l/min).

2.2.5 Definition of angiographic radial artery spasm

Angiography of the radial artery was performed after insertion of the introducer sheath, after injection of normal saline 10 ml with nitroglycerine 200μg and before withdrawal of introducer sheath. A 30 to 40-mm long segment of radial artery from the tip of the introducer sheath was selected for the determination of the mean diameter of the vessel using a computer-assisted quantification method (GE® medical QCA, USA). Internal diameter of the 5-Fr. introducer sheath was used as a reference. We defined the reference diameter of radial artery as the mean diameter of radial artery after nitroglycerine injection. Angiographic RAS was defined when the diameter stenosis is 50% or more by using the following equation: Diameter stenosis (%) at the start of the procedure = (reference diameter – minimal radial artery diameter after inserting sheath introducer) / reference diameter; Diameter stenosis (%) at the end of the procedure = (reference diameter – minimal radial artery diameter before withdrawing sheath introducer) / reference diameter.

2.2.6 Definition of clinical radial artery spasm

The operator accessed the RAS on the basis of a questionnaire addressing the following four signs: persistent forearm pain, pain response on catheter manipulation, pain response to introducer withdrawal and difficult catheter manipulation after being trapped by the radial artery. Clinical RAS was considered to be indicated by the presence of at least 2 of these 4 signs or when the operator considered it was necessary to administer a second dose of the spasmolytic agent.

2.2.7 Statistical analysis

This study was designed to test whether EMLA cream could reduce the RAS during TRA. The incidence of the RAS was assumed to be 20% in control group and 5% in EMLA group according to the results of previous studies.[5,6] For inequality tests for two proportion with a power of 80% and two-sided α level of .05, we estimated that 75 subjects were needed in each group

The statistical analysis was performed with the SPSS version 15 software (SPSS, Inc., Chicago, Illinois). Continuous variables were expressed as the mean ± standard deviation, and categorical data as number (percentage). To compare the values between two groups,

we used Student's *t* test for the continuous variables, whereas the chi-square test for the categorical variables.

3. Results

3.1 Baseline characteristics

A total of 76 subjects were enrolled in this study. Each group consisted of 38 subjects. The baseline characteristics of the subjects including age, sex, past history, medication, approach site, anthropometric data, sympathetic tone at baseline and diameter of radial artery were not different between two groups. Baseline characteristics were presented at table 1.

Table 1. Baseline characteristics

	EMLA group (n=38)	Control group (n=38)	*p*
Age	55 ± 9	53 ± 8	0.43
Male	23 (60.5)	24 (63.2)	1.00
Past History			
Hypertension	22 (57.9)	17 (44.7)	0.36
Diabetes	8 (21.1)	9 (23.7)	1.00
Dyslipidemia	5 (13.2)	12 (31.6)	0.10
Previous MI	1 (2.6)	2 (5.3)	1.00
Previous PCI	2 (5.3)	6 (15.8)	0.26
Cerebral infarction	3 (3.9)	2 (5.3)	1.00
Smoking	23 (60.5)	21 (55.3)	0.30
Current	6 (15.8)	10 (26.3)	
Ex-smoker	17 (44.7)	11 (28.9)	
Medication			
Beta blocker	7 (18.4)	7 (18.4)	1.00
ACE inhibitor or ARB	10 (26.3)	9 (23.7)	1.00
Calcium channel blocker	2 (5.3)	4 (10.5)	0.67
Nitrate	15 (39.5)	15 (39.5)	1.00
Approach site			
Left radial artery	22 (57.9)	30 (78.9)	0.08
Anthropometric data			
Height, cm	163 ± 8	163 ± 9	0.79
Weight, kg	68 ± 11	68 ± 11	0.92
BSA, m^2	1.75 ± 0.18	1.75 ± 0.18	0.98
BMI, kg/m^2	25 ± 3	25 ± 3	0.73
Sympathetic tone at baseline			
SBP, mmHg	146 ± 22	143 ± 24	0.54
DBP, mmHg	79 ± 11	80 ± 17	0.78
MAP, mmHg	101 ± 13	101 ± 18	0.90
PR, beat/min	72 ± 16	69 ± 12	0.41
SV, ml	82.7 ± 31.5	72.0 ± 32.5	0.15
CO, l/min	13.2 ± 5.2	12.9 ± 7.8	0.14
TPR, mmHg·l/min	13.2 ± 5.2	12.9 ± 7.8	0.87
Diameter of radial artery*, mm	2.42 ± 0.44	2.26 ± 0.46	0.11

MI, myocardial infarction; PCI, percutaneous coronary intervention; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BSA, body surface area; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP; mean arterial pressure; PR, pulse rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance,

* Diameter of radial artery after nitroglycerine injection

3.2 Score of radial pain during the procedure

Radial pain measured by VAS and VRS-4 during lidocaine infiltration was significantly lower in EMLA group (VAS: 3.1 ± 1.7 vs. 4.0 ± 1.7, $p = 0.04$; VRS-4: 2.0 ± 0.5 vs. 2.2 ± 0.5, $p = 0.03$). But radial pain during insertion of introducer sheath was not different between two groups (VAS: 2.5 ± 2.3 vs. 3.3 ± 2.5, $p = 0.15$; VRS-4: 1.8 ± 0.7 vs. 2.1 ± 0.8, $p = 0.10$). The score of radial pain during procedure was presented at table 2.

Table 2. The score of radial pain during procedure

	EMLA group	Control group	*p*
Visual analogue scale			
Pain during lidocaine infiltration	3.1 ± 1.7	4.0 ± 1.7	0.04
Pain during introducer sheath insertion	2.5 ± 2.3	3.3 ± 2.5	0.15
4-category verbal rating scale			
Pain during lidocaine infiltration	2.0 ± 0.5	2.2 ± 0.5	0.03
Pain during introducer sheath insertion	1.8 ± 0.7	2.1 ± 0.8	0.10

3.3 Sympathetic response

The sympathetic tone including SBP, DBP, MAP, PR, SV, CO and TPR were not different between two groups at baseline, after lidocaine infiltration, after artery puncture and after sheath insertion (table 3).

Table 3. Sympathetic tone parameters at baseline, after lidocaine infiltration, after artery puncture and after sheath insertion

	EMLA group	Control group	*p*
Mean SBP, mmHg			
At baseline	146 ± 22	143 ± 24	0.54
After lidocaine infiltration	151 ± 25	156 ± 25	0.37
After artery puncture	152 ± 26	151 ± 30	0.91
After sheath insertion	145 ± 25	149 ± 31	0.57
Mean DBP, mmHg			
At baseline	79 ± 11	80 ± 17	0.78
After lidocaine infiltration	81 ± 14	87 ± 20	0.12
After artery puncture	80 ± 13	84 ± 19	0.28
After sheath insertion	78 ± 11	84 ± 21	0.11
Mean MAP, mmHg			
At baseline	101 ± 13	101 ± 18	0.90
After lidocaine infiltration	104 ± 15	110 ± 20	0.16
After artery puncture	104 ± 15	106 ± 21	0.55
After sheath insertion	100 ± 13	106 ± 23	0.21
Mean PR, mmHg			
At baseline	72 ± 16	69 ± 12	0.31
After lidocaine infiltration	73 ± 16	77 ± 19	0.81
After artery puncture	71 ± 16	72 ± 13	0.94
After sheath insertion	72 ± 16	72 ± 13	0.14
Mean SV, ml			
At baseline	83 ± 32	72 ± 33	0.15
After lidocaine infiltration	86 ± 33	92 ± 36	0.43
After artery puncture	85 ± 31	87 ± 35	0.79
After sheath insertion	83 ± 31	83 ± 34	0.96
Mean CO, l/min			
At baseline	5.8 ± 2.2	5.0 ± 2.1	0.14
After lidocaine infiltration	5.9 ± 2.3	6.5 ± 2.3	0.26
After artery puncture	5.5 ± 2.0	5.9 ± 2.3	0.45
After sheath insertion	5.4 ± 1.9	5.6 ± 2.2	0.79
Mean TPR, mmHg·l/min			
At baseline	13.2 ± 5.2	12.9 ± 7.8	0.87
After lidocaine infiltration	14.2 ± 6.2	18.8 ± 13.2	0.06
After artery puncture	14.0 ± 6.0	17.1 ± 11.8	0.16
After sheath insertion	13.2 ± 5.1	16.9 ± 14.8	0.14

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP; mean arterial pressure; PR, pulse rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance,

But the sympathetic response was significantly blunted in EMLA group from baseline to lidocaine infiltration (ΔSBP, mmHg: 5 ± 10 vs. 13 ± 12, $p < 0.01$; ΔDBP, mmHg: 2 ± 8 vs. 7 ± 12, $p = 0.03$; ΔMAP, mmHg: 3 ± 8 vs. 9 ± 10, $p < 0.01$; ΔPR, beat/min: 2 ± 4 vs. 8 ± 14, $p < 0.01$; ΔSV, ml: 3 ± 6 vs. 21 ± 17, $p < 0.01$; ΔCO, l/min: 0.2 ± 4.8 vs. 1.5 ± 1.4 $p < 0.01$ ΔTPR, mmHg·l/min; 1.0 ± 3.2 vs. 5.9 ± 8.2, $p < 0.01$). There was no difference of sympathetic response from lidocaine infiltration to puncture and from puncture to sheath insertion except SBP from lidocaine infiltration to puncture (ΔSBP, mmHg: 0 ± 9 vs. -5 ± 14, $p = 0.04$). The change of sympathetic tone during procedure was presented in table 4.

Figure 3 illustrated the average and the absolute change of sympathetic tone parameters during procedure.

Table 4. Absolute change of sympathetic tone parameters from baseline to lidocaine infiltration, from lidocaine infiltration to puncture and from puncture to sheath insertion

	EMLA group	Control group	*p*
ΔSBP, mmHg			
From baseline to lido. infiltration	5 ± 10	13 ± 12	< 0.01
From lido. infiltration to puncture	0 ± 9	-5 ± 14	0.04
From puncture to sheath insertion	-7 ± 12	-2 ± 13	0.13
ΔDBP, mmHg			
From baseline to lido. infiltration	2 ± 8	7 ± 12	0.03
From lido. infiltration to puncture	-1 ± 7	-3 ± 10	0.33
From puncture to sheath insertion	-3 ± 6	0 ± 10	0.27
ΔMAP, mmHg			
From baseline to lido. infiltration	3 ± 8	9 ± 10	< 0.01
From lido. infiltration to puncture	0 ± 6	-4 ± 10	0.10
From puncture to sheath insertion	-4 ± 7	-1 ± 11	0.16
ΔPR, beat/min			
From baseline to lido. infiltration	2 ± 4	8 ± 14	< 0.01
From lido. infiltration to puncture	-2 ± 5	-5 ± 16	0.24
From puncture to sheath insertion	1 ± 4	0 ± 4	0.24
ΔSV, ml			
From baseline to lido. infiltration	3 ± 6	21 ± 17	< 0.01
From lido. infiltration to puncture	-1 ± 8	-6 ± 14	0.11
From puncture to sheath insertion	-2 ± 5	-4 ± 11	0.20
ΔCO, l/min			
From baseline to lido. infiltration	0.2 ± 4.8	1.5 ± 1.4	< 0.01
From lido. infiltration to puncture	-0.4 ± 0.7	-0.7 ± 1.1	0.32
From puncture to sheath insertion	-0.1 ± 0.8	-0.3 ± 1.0	0.24
ΔTPR, mmHg·l/min			
From baseline to lido. infiltration	1.0 ± 3.2	5.9 ± 8.2	< 0.01
From lido. infiltration to puncture	-0.2 ± 3.4	-1.7 ± 6.7	0.22
From puncture to sheath insertion	-0.8 ± 2.1	-0.1 ± 5.5	0.45

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP; mean arterial pressure; PR, pulse rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; Lido, lidocaine.

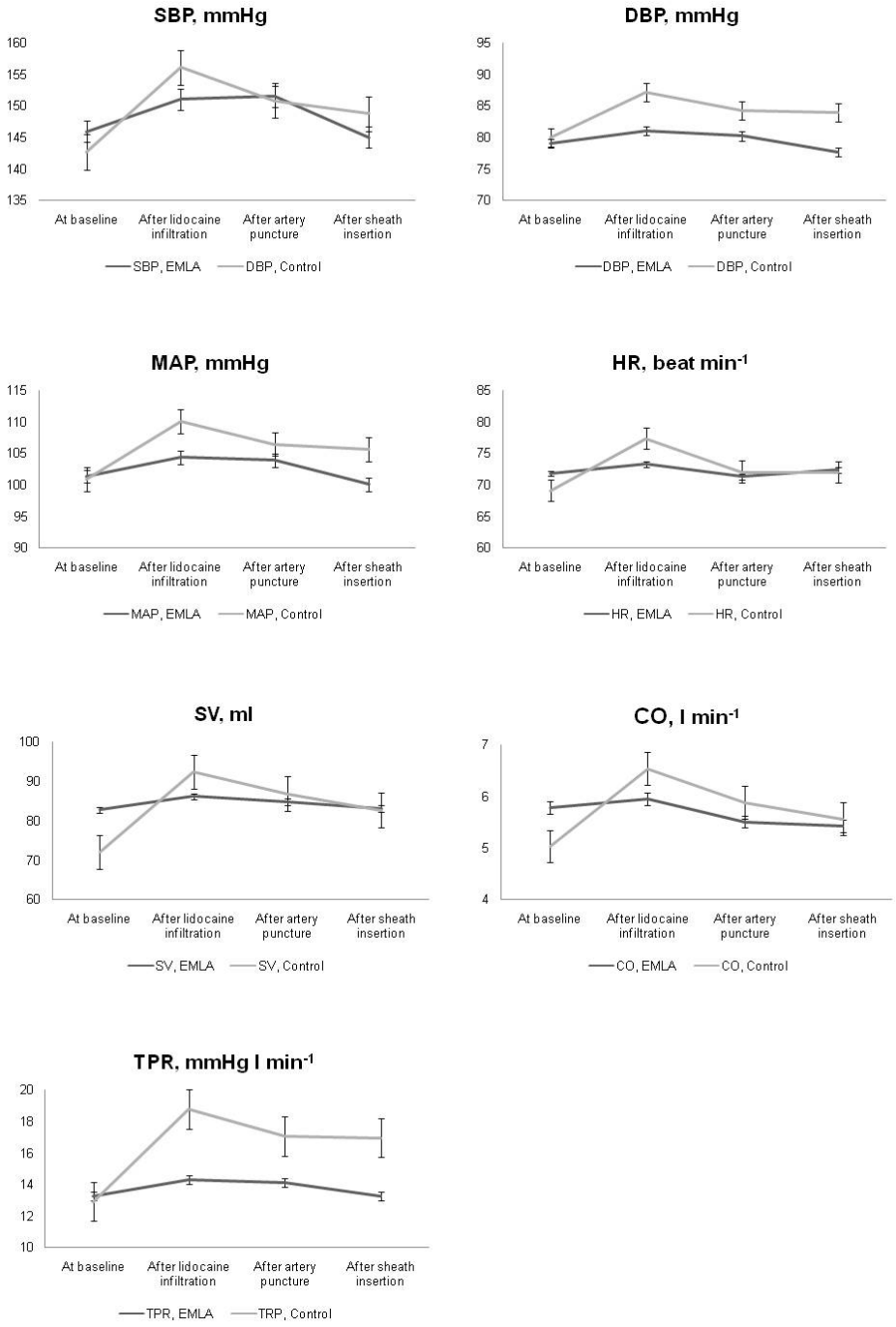

Figure 3. Average and absolute change of sympathetic tone parameters during procedure

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP; mean arterial pressure; PR, pulse rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance,

3.4 Clinical and angiographic radial artery spasm

The incidence of clinical or angiographic RAS was lower in EMLA group without statistical significance (Angiographic RAS at the start of procedure, n (%): 2 (5.3) vs. 6 (15.8), $p = 0.26$; Clinical or angiographic RAS at the end of procedure, n (%): 5 (13.2) vs. 9 (23.7), $p = 0.38$). And minimal luminal diameter at the start of procedure was significantly larger in EMLA group (1.78 ± 0.54 mm vs. 1.51 ± 0.41 mm, $p = 0.02$). Clinical and angiographic radial artery spasm was presented at table 5.

Table 5. The result of clinical and angiographic radial artery spasm

	EMLA group	Control group	*p*
At the start of procedure			
Angiographic RAS, n (%)	2 (5.3)	6 (15.8)	0.26
MLD, mm	1.78 ± 0.54	1.51 ± 0.41	0.02
DS, %	27.1 ± 15.4	32.3 ± 16.4	0.16
At the end of procedure			
Clinical or angiographic RAS, n (%)	5 (13.2)	9 (23..7)	0.38
Clinical RAS, n (%)	3 (7.9)	4 (10.5)	1.00
Persistent forearm pain	1 (2.6)	1 (2.6)	1.00
Pain response on catheter manipulation	2 (5.3)	3 (7.9)	1.00
Pain response to introducer withdrawal	4 (10.5)	5 (13.2)	1.00
Difficult catheter manipulation	0 (0)	1 (2.6)	1.00
Need of 2nd vasodilator injection	1 (2.6)	2 (5.3)	1.00
Angiographic RAS, n (%)	2 (5.3)	6 (15.8)	0.26
MLD, mm	1.92 ± 0.57	1.73 ± 0.41	0.14
DS, %	21.8 ± 20.0	20.5 ± 21.1	0.81

RAS, radial artery spasm; MLD, minimal luminal diameter; DS, diameter stenosis; SD, standard deviation

4. Discussion

Our study showed that the EMLA cream effectively reduced the radial pain measured by VAS and VRS-4 during lidocaine infiltration and could reduce the sympathetic response presented by blunted increment of SBP, DBP, MAP, PR, SV, CO and TPR measured by Finometer. But these hemodynamic benefits were disappeared after lidocaine infiltration. Although we failed to demonstrate that EMLA cream could reduce the pre-defined angiographic or clinical RAS, minimal luminal diameter was significantly larger and incidence of RAS at the start of the procedure was lower in EMLA group.

RAS is the most frequent complication of TRA and can cause significant discomfort to the patient and reducing the procedural success rate.[3,4] Even in centers where there is extensive experience with the radial route, RAS occurs in 15 to 30% of the TRA procedure.[5,6] The RAS may be related to radial artery anatomical anomalies, moderate-to-severe pain during radial artery cannulation, small diameter of radial artery, prolonged cannulation, ratio of the radial artery diameter to the sheath outer diameter and anticoagulation during arterial cannulation.[8,14]

The radial artery is a thick-walled vessel composed mainly of smooth muscle cells

arranged in concentric layers. This marked muscular component of the artery, together with the high density of α_1 receptors, makes this vessel especially susceptible to spasms.[7] So, we hypothesized that reducing the radial pain can reduce the α_1 receptor activation by the catecholamine release and could reduce the RAS.

The effect of EMLA cream on reducing the radial pain is well known by several studies.[9,15,16] Our study result also showed significant reduction of radial pain measured by VAS and VRS-4. But, it is the most remarkable finding of our study that we evaluated the sympathetic response by means of measuring SBP, DBP, MAP, PR, SV, CO and TPR with using non-invasive monitoring. Our study showed significant blunted sympathetic response in EMLA group during lidocaine infiltration. Although we did not measure plasma catecholamines such as epinephrine and norepinephrine, these analyses are challenging because there are lack of specificity and reproducibility and physiological limitations.[17] We could also observe that the effect of EMLA cream on sympathetic response was disappeared after lidocaine infiltration. The reason for this result is that the lidocaine infiltration has as much as effect on reducing the radial pain and this fact make no difference in radial pain and sympathetic response between two groups after lidocaine

infiltration.

Activation of α receptor results in peripheral vasoconstriction and thus increases peripheral vascular resistance. This mechanism can lead to increase diastolic blood pressure. In addition, activation of β receptor results in increment of heart rate and stroke volume and thus increases cardiac output. This mechanism leads to increase systolic blood pressure. We observed that all parameters related to sympathetic tone increased after noxious stimuli. Interestingly, we could also observe that the time to peak was not simultaneous among the parameters as shown in figure 1. Although we could not analyses time interval among the parameters related to sympathetic tone in all subjects, we could observe that sequence of increment of sympathetic tone was not similar among selected subjects. For example, increment of pulse rate preceded increment of peripheral resistance in some subjects. In contrary, increment of peripheral resistance preceded increment of pulse rate. We could presume that sequence of sympathetic response is different among the subjects and this could be the mechanism of difference in RAS development. But further study is needed to confirm this hypothesis.

We already defined angiographic RAS when the diameter reduction at the start of the

procedure or at the end of the procedure is 50% or more compared to reference diameter. Our study fail to demonstrate that EMLA cream could reduce the pre-defined angiographic RAS. But, we could observe that minimal luminal diameter at the start of the procedure was significantly larger in EMLA group despite of similarity in reference diameter and low incidence of RAS in EMLA group without statistical significance. At the step of the sample size calculation, we assumed 15% difference in RAS between two groups. So, if we increase the sample size, it is expected that we can find the benefit of EMLA cream on RAS. In contrast with this, we could not find any difference in RAS between two groups at the end of the procedure. The reasons for this result could be explained followings. First, we infiltrated lidocaine after applying the study cream in two groups. Second, multiple factors such as number of trials of radial artery puncture, type of catheter, total procedure time, emotional status and et al are responsible for RAS. Because lidocaine itself is another analgesic and multiple factors are related to RAS, prevention of RAS only by reducing radial pain could not be observed between two groups at the end of the procedure.

A limitation of EMLA cream is the delay necessary to obtain anesthesia. Skin

preparation of topical anesthestics is time-dependent, and depth of dermal anesthesia is approximately 5 mm after 90 min.[15] On contrary, prolonged applying time after 4 hours before procedure, it is impossible to reduce the radial pain.[9] So, it should be considered that EMLA cream is effective in reducing wrist pain when the application time is 1 to 3 hours before the procedure.

5. Conclusion

Our study demonstrated that the EMLA cream could effectively reduce the wrist pain and sympathetic response including SBP, DBP, MAP, PR, SV, CO and TPR during lidocaine infiltration. In addition, we could also observe the benefit of EMLA cream on RAS at the start of the procedure in term of larger minimal luminal diameter.

For the convenience of patients and prevention of RAS, EMLA cream should be considered when the TRA is planned.

References

1. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am Heart J 157:132–140, 2009

2. Agostoni P, Biondi-Zoccai GG, de Benedictis ML, Rigattieri S, Turri M, Anselmi M, Vassanelli C, Zardini P, Louvard Y, Hamon M. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures: systematic overview and interventional procedures. J Am Coll Cardiol 44:349–356, 2004

3. Goldberg SL, Renslo R, Sinow R, French WJ. Learning curve in the use of the radial artery as vascular access in the performance of percutaneous transluminal coronary angioplasty. Cathet Cardiovasc Diagn 44:147–152, 1998

4. Hildick-Smith D, Lowe M, Walsh J, Ludman PF, Stephens NG, Schofield PM, Stone DL, Shapiro LM, Petch MC. Coronary angiography from the radial artery: experience, complications and limitations. Int J Cardiol 15:231–239, 1998

5. Hildick-Smith DJ, Walsh JT, Lowe MD, Shapiro LM, Petch MC. Transradial

coronary angiography in patients with contraindications to the femoral approach: An analysis of 500 cases. Catheter Cardiovasc Interv 61:60–66, 2004

6. Kiemeneij F, Vajifdar BU, Eccleshall SC, Laarman G, Slagboom T, van der Wieken R. Evaluation of a spasmolytic cocktail to prevent radial artery spasm during coronary procedures. Catheter Cardiovasc Interv 58:281–284, 2003

7. He G-W, Yang C-Q. Characteristics of adrenoreceptors in the human radial artery. J Thorac Cardiovasc Surg 115:1136–1141, 1998

8. Ruiz-Salmerón RJ, Mora R, Vélez-Gimón M, Ortiz J, Fernández C, Vidal B, Masotti M, Betriu A. Radial artery spasm in transradial cardiac catheterization. Assessment of factors related to its occurrence, and of its consequences during follow-up. Rev Esp Cardiol 58:504-511, 2005

9. Kim JY, Yoon J, Yoo BS, Lee SH, Choe KH. The effect of a eutectic mixture of local anesthetic cream on wrist pain during transradial coronary procedures. J Invasive Cardiol 19:6-9, 2007

10. Todd KH, Funk KG, Funk FP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 27:485–489, 1996

11. Imholz BP, Wieling W, van Montfrans GA, Wesseling KH. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. Cardiovasc Res 38:605–616, 1998

12. Guelen I, Westerhof BE, van der Sar GL, van Montfrans GA, Kiemeneij F, Wesseling KH, Bos WJ. Finometer, finger pressure measurements with the possibility to reconstruct brachial pressure. Blood Press Monit 8:27–30, 2003

13. Bogert LW, van Lieshout JJ. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. Exp Physiol 90:437–446, 2005

14. Fukuda N, Iwahara S, Harada A, Yokoyama S, Akutsu K, Takano M, Kobayashi A, Kurokawa S, Izumi T. Vasospasms of the radial artery after the transradial approach for coronary angiography and angioplasty. Jpn Heart J 45:723-731, 2004

15. Joly LM, Spaulding C, Monchi M, Ali OS, Weber S, Benhamou D. Topical lidocaine-prilocaine cream (EMLA) versus local infiltration anesthesia for radial artery cannulation. Anesth Analg 87:403-406, 1998

16. Smith M, Gray BM, Ingram S, Jewkes DA Double-blind comparison of topical lignocaine-prilocaine cream (EMLA) and lignocaine infiltration for arterial

cannulation in adults. Br J Anaesth 65:240-242, 1990

17. Hjemdahl P. Plasma catecholamines--analytical challenges and physiological limitations. Baillieres Clin Endocrinol Metab 7:307-353, 1993

국문 요약

요골동맥을 이용한 관상동맥 조영술 중 국소 마취 (EMLA) 크림의 교감 신경계 반응 및 요골 동맥 연축에 대한 효과

< 지도 윤 정 한 교수 >

연세대학교 대학원 의학과

윤 영 진

배경: 요골 동맥 연축은 요골 동맥을 이용한 관상동맥 조영술에서 가장 흔한 합병증 중 하나이다. 주로 카테콜라민에 의해 요골 동맥의 연축이 발생하며 시술 중 발생하는 요골 부위의 통증이 교감 신경계를 항진시켜 카테콜라민의 분비를 증가시키게 된다. 이에 저자는 국소 마취 (EMLA) 크림이 요골 동맥을

이용한 관상동맥 조영술 중에 요골 부위의 통증 및 교감신경계에 미치는 영향을 알아보고자 하였다. **방법:** 요골 동맥을 이용한 관상동맥을 시행받은 76명의 환자를 대상으로 하였다. 관상동맥 조영술 전에 손목 부위에 EMLA 크림을 도포하는지 여부에 따라 EMLA군과 대조군으로 무작위 배정되었다. 요골 부위 통증은 visual analogue scale (VAS)와 verbal rating scale (VRS-4)를 이용하여 국소 마취 주사제 투여 및 유도관 삽입 시에 평가하였다. 교감 신경계의 반응은 수축기(SBP) 및 이완기 혈압 (DBP), 평균동맥압(MAP), 맥박 수(PR), 일회박출량(SV), 심박출량(CO)과 총말초저항(TPR)을 이용하였고, 최초 시술 전, 국소 마취 주사제 투여 후, 동맥 천자 후, 유도관 삽입 후에 각각 평가하였다. 요골 동맥의 연축은 미리 정의된 임상 및 혈관 조영의 기준에 의하여 평가하였다. **결과:** 양군에서의 성별, 연령, 과거력, 약물 투여력, 접근 경로, 신체 계측 정보, 최초 교감 신경계 긴장 정도 및 요골 동맥의 직경에는 차이가 없었다. 요골 부위 통증은 EMLA군에서 국소 마취 주사제 투여 단계에서 유의하게 낮았다 ((VAS: 3.1 ± 1.7 vs. 4.0 ± 1.7, $p = 0.04$; VRS-4: 2.0 ± 0.5 vs. 2.2 ± 0.5, $p = 0.03$). 교

감신경계 반응은 EMLA군에서 유의하게 낮았다 (ΔSBP, mmHg: 5 ± 10 vs. 13 ± 12, $p < 0.01$; ΔDBP, mmHg: 2 ± 8 vs. 7 ± 12, $p = 0.03$; ΔMAP, mmHg: 3 ± 8 vs. 9 ± 10, $p < 0.01$; ΔPR, beat/min: 2 ± 4 vs. 8 ± 14, $p < 0.01$; ΔSV, ml: 3 ± 6 vs. 21 ± 17, $p < 0.01$; ΔCO, l/min: 0.2 ± 4.8 vs. 1.5 ± 1.4 $p < 0.01$ ΔTPR, mmHg·l/min; 1.0 ± 3.2 vs. 5.9 ± 8.2, $p < 0.01$). 임상 및 혈관 조영을 이용한 요골 동맥 연축은 양군에서 차이가 없었으나 유도관 삽입 직후의 최소 혈관 직경(minimal luminal diameter, MLD)은 EMLA 군에서 유의하게 컸다(1.78 ± 0.54 mm vs. 1.51 ± 0.41 mm, $p = 0.02$). **결론:** 본 연구를 통해 EMLA 크림이 국소 마취 주사제 투여 동안의 요골 부위 통증 및 교감 신경계 항진을 유의하게 낮출 수 있었다. EMLA 군에서 유도관 삽입 직후 MLD가 더 크게 관찰되어 EMLA 크림이 요골 동맥 연축 예방에 도움이 될 것으로 기대된다.

핵심단어: 국소 마취; 관상동맥 조영; 요골 동맥