The effect of preprocedural application of topical medications on the radial artery dilation and occurrence of vasospasm in patients undergoing transradial angiography

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Diploma thesis

Academic year:
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First and foremost, I would like to express my gratitude to my mentor Josip A. Borovac, MD, PhD for his guidance, dedication, and help in writing my diploma thesis.
I would also like to thank my friends for believing in me and being there for all these years.
Finally, I'd like to express my eternal gratitude to my parents and my brother for their unconditional love, guidance, and support. Thank you for always believing in me.

LIST OF ABBREVIATIONS

ACC - *American College of Cardiology*

ACS – *Acute coronary syndrome*

AHA - *American Heart Association*

CAD – *Coronary artery disease*

CCS - *chronic coronary syndrome*

ESC – *European Society of Cardiology*

LRA – *Left radial artery*

NSTEMI – *Non-ST segment elevation myocardial infarction*

PCI – *Percutaneous coronary intervention*

TFA – *Transfemoral access*

TRA – *Transradial access*

RAO – *Radial artery occlusion*

RAS – *Radial artery spasm*

RCT – *Randomized controlled trial*

RRA – *Right radial artery*

PCI – *Percutaneous coronary intervention*

STEMI – *ST-segment elevation myocardial infarction*

VAS – *Visual analogue scale*

1. INTRODUCTION

1.1. History of coronary angiography

When it is clinically necessary to identify the presence of ischemic/atherosclerotic coronary heart disease that cannot be adequately assessed by non-invasive methods, diagnostic cardiac catheterization as the gold-standard invasive procedure is indicated. Experienced operators can perform cardiac catheterization safely as the risk of a significant complications is less than 1% and mortality is less than 0,08% in the elective non-acute setting (1).

Currently used for both diagnostic and frequently therapeutic objectives, cardiac catheterization is a combination of hemodynamic and angiographic treatment. The choice to do a cardiac catheterization must be based on a thorough balancing of the procedural risks *versus* the patient's expected benefit, as it is the case with any invasive procedure in medicine. The American Heart Association (AHA) and the American College of Cardiology (ACA) have created indications for the use of coronary intervention and catheterization in the therapy of stable angina, unstable angina, and ST-elevation myocardial infarction (2). Similarly, European Society of Cardiology (ESC) has published several important guidelines that address acute coronary syndrome (ACS), chronic coronary syndrome (CCS), and myocardial revascularization strategies in various clinical scenarios (3-5).

Transradial access was introduced early in the development of cardiac catheterization procedures, despite the transfemoral route to cardiac catheterization being dominant for decades (6). Using a radial artery cut-down with 8- to 10-F catheters, Radner (7) provided one of the earliest accounts of transradial central arterial catheterization and efforts at coronary artery imaging in 1948. Despite initial enthusiasm for the transradial technique, technological limits forced a move to bigger arteries like the brachial, carotid, and femoral systems. The first description of the radial artery used in coronary angiography was by Campeau in 1989 (8). In 1993, Ferdinand Kiemeneij and Laarman (9) published the first study on the transradial coronary stenting method. There were a few enthusiastic early adopters due to the documented decreases in periprocedural bleeding and the reported improvements in patient comfort with this procedure, but the transradial approach remained primarily a specialized technique for many years to come (6).

1.2 Radial access artery anatomy

Because it has been linked to significant decrease in periprocedural complications, reduced hospital stay, and showed to be preferential to patients, using the radial artery as an access route for neurointerventional operations has gained popularity. Transradial access (TRA) does, however, provide a special set of safety issues, including extensive familiarity with the anatomical variations of the upper extremity arterial supply (10).

The radial artery starts in the cubital fossa, where the bifurcation of the brachial artery occurs, resulting in the dual vascular supply of the forearm by the ulnar and radial artery. At the anterior border of the radius and medial to the tendon of the *flexor carpi radialis*, the radial artery can be felt as it descends along the lateral side of the forearm above the radius toward the wrist. Transradial procedures may be affected by a number of variations in the radial artery's origin or course, whereas the distal forearm, where cannulation is typically done, exhibits less anatomic variation (11). Branches of the radial artery includes the recurrent radial artery arising just beyond the origin of the radial artery on the lateral aspect. Around the elbow joint it ends by anastomosing with branches of the profunda brachii artery. This arterial branch is of particular importance as perforation commonly occurs at this site. In case of radial artery occlusion or thrombosis, the palmar carpal branch provide collateral circulation due to its anastomosis with the ulnar palmar carpal branch, anterior interosseous artery and recurrent branches of the deep palmar arch (10). From the wrist's second segment, the radial artery verses laterally while giving rise to the superficial palmar branch, which arises proximally to the anatomic snuffbox. This branch anastomoses with the corresponding ulnar branch completing the superficial palmar arch. In the terminal part the deep palmar branch arises, forming the deep palmar arch as it joins with the corresponding ulnar branch. In the hand the radial artery gives rise to the princeps pollicis artery and radialis indicis artery (10).

The size of the radial artery at its usual access location, has a mean diameter of 2,43 +/- 0,38 mm in females and 2,69 +/-0,40 mm in males (10). Access site-related radial artery spasm or thrombosis/occlusion occurs in higher rate in TRA, and, in fact, documented small size of the radial artery might be considered as a relative contraindication to perform catheterization procedure via transradial route (10,11). Calcium channel blockers, nitrates and heparin tend to be a widely used as pharmacological prophylaxis (so-called radial cocktail) and complex high-risk interventions requiring larger than 6 French sheaths might sometimes consider using the TFA as access site (10). However, radial access should be utilized for the purpose of coronary angiography whenever possible as it demonstrated clear advantages over transfemoral route.

Variants of the radial artery that are common are shown below in Figure 1 and Table 1.

Table 1. Anatomical considerations for transradial catheterization

Table 1 Anatomic considerations for transradial catheterization

Anatomic variant	Incidence	Importance	Reference
Radial artery loop	1% (n=997)	Can cause artery avulsion if straightened; increases conversion from radial to femoral access	26
High origin of the radial artery/'brachioradial artery'	9.2% (n=120)	Increases risk of spasm due to small size of artery, can risk dissection when exchanging from a hydrophilic to stiff guidewire	22
Aberrant right subclavian artery	0.47% (n=6833)	Difficulty entering the ascending aorta when using a transradial approach	31
Tortuous right brachiocephalic artery	25% (n=52)	Increases difficulty in vessel selection due to loss of distal catheter control in tortuous vessel	32
Bovine aortic arch	13.6% (n=23 882)	Eases catheterization of left common carotid artery from right transradial approach, may increase difficulty of left common carotid artery catheterization from transfemoral approach	32

Taken from Narsinh K, Mirza M, Duvvuri M, Caton Jr M, Baker A, Winkler E et al. Radial artery access anatomy: considerations for neuroendovascular procedures. *Journal of NeuroInterventional Surgery* (10)

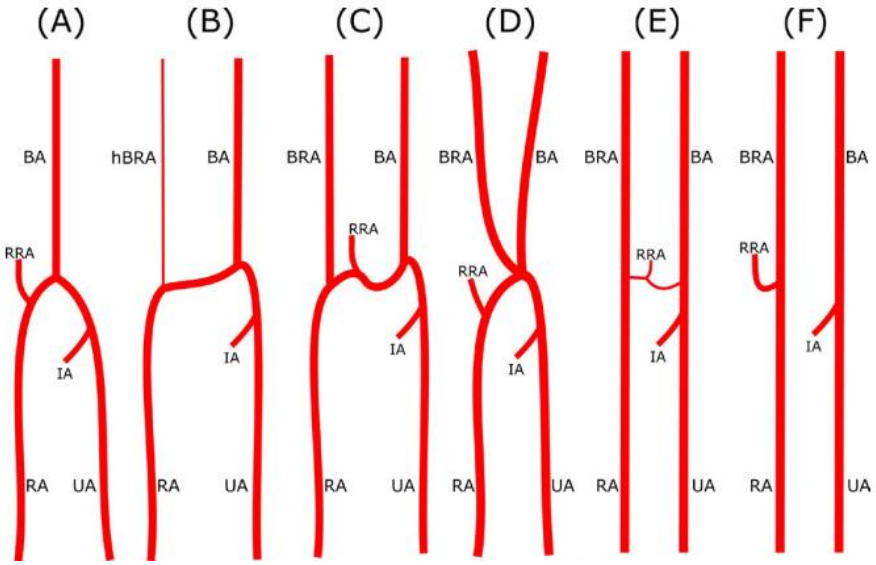

Figure 1. Radial artery anatomic variants

Taken from Narsinh K, Mirza M, Duvvuri M, Caton Jr M, Baker A, Winkler E et al. Radial artery access anatomy: considerations for neuroendovascular procedures. *Journal of NeuroInterventional Surgery* (10)

The anatomical variants depicted in Figure 1 involve the brachioradial artery, which has a prevalence of nearly 10%. They increase the risk of developing vascular complications when performing TRA, and it is of importance that the operator detects these variants to perform a safe and effective procedure.

1.3. Advent of radial artery access for coronary angiography procedures

As noted earlier, the first description of the radial artery being utilized in efforts of coronary artery imaging happened in 1948 (7). From these initial findings, a breakthrough in using radial access happened as the first transradial coronary angiography was described in 1989 (8) followed by the first delivery and implantation of coronary stent via radial route in 1992 (9). Three decades have passed since the first angiography and coronary stenting, and it is rapidly becoming favorable to utilize the radial artery as site of access when performing percutaneous coronary intervention and selective coronary angiography (12). In 2015, TRA was recommended in the guidelines of the European Society of Cardiology (ESC) as the preferred access method in managing ACS (13).

PCI using the radial artery access has shown to be associated with lower vascular and bleeding complications than interventions utilizing the transfemoral route. This has been shown to be particularly true for patients with ACS (14).

Multiple research efforts and clinical trials are further supporting the reduced adverse outcome in using TRA over TFA for PCI. For example, the MATRIX trial, a large randomized controlled trial by Valgimigli et.al. concluded that compared to femoral access, radial access was significantly associated with lower rates of net unfavorable clinical outcomes in individuals with ACS. It is nowadays clear that when invasive management is performed, radial access should be the standard method of choice (15). Valgimigli and colleagues also published a large randomized multicentre trial (16) showing reduced major bleeding events and all-cause mortality when comparing TRA to TFA. It has also been demonstrated that vascular complications and bleeding events are even more reduced in patients with STEMI undergoing TRA (17,18). Mason and colleagues (11) published a large and seminal meta-analysis deriving data from 19 clinical trials with a total of 21,134 patients included. The main endpoints analyzed in this meta-analysis were mortality, major bleeding, and vascular complications. The results of this important study are shown in Figure 2, Figure 3 and Figure 4.

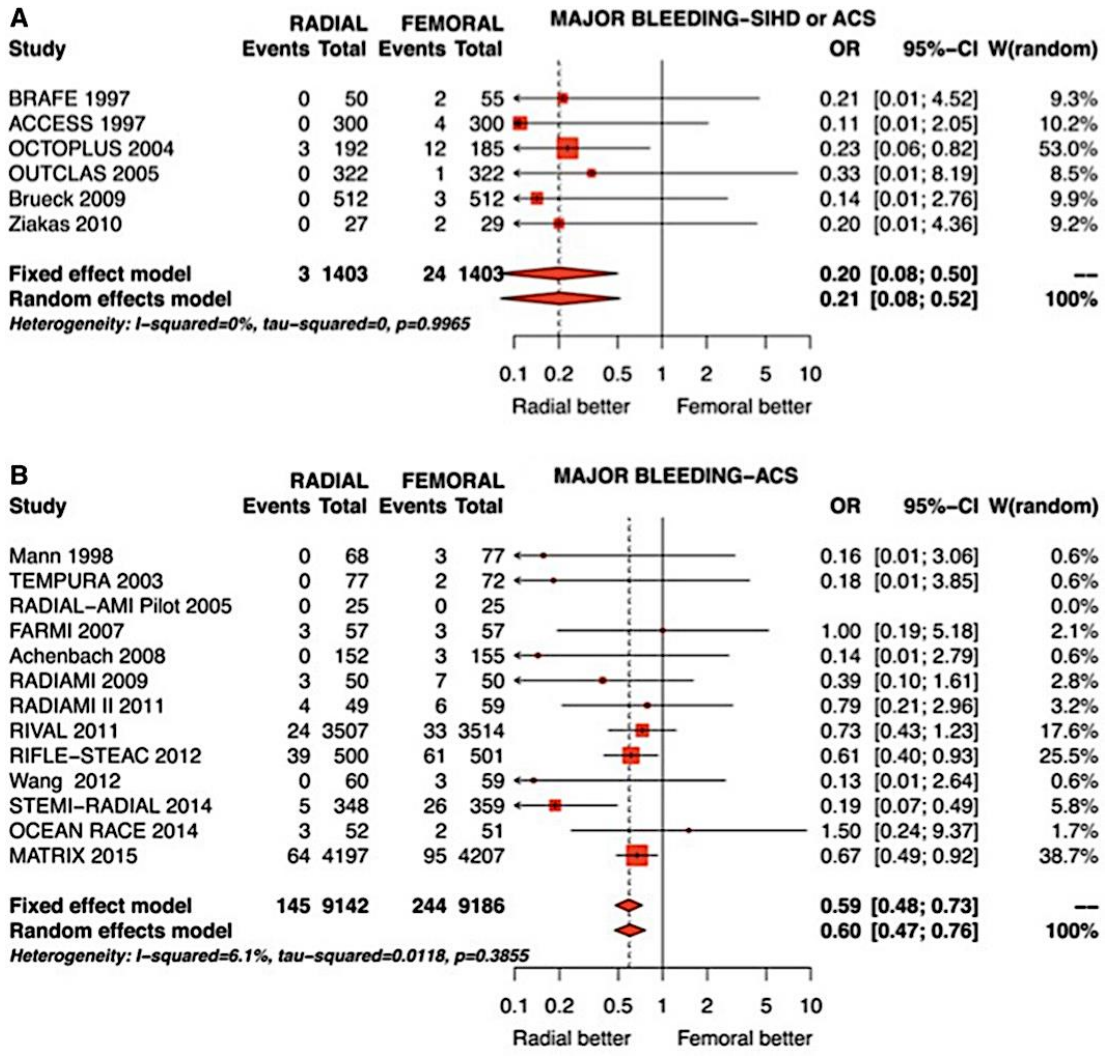

Figure 2. Rates of major bleeding at 30 days or longest follow-up after TRA or TFA PCI in trials enrolling patients with (A) ACS or stable ischemic heart disease or (B) only ACS

Figure obtained from the work by Mason P, Shah B, Tamis-Holland J, Bittl J, Cohen M, Safirstein J et al. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. *Circulation: Cardiovascular Interventions*. 2018;11(12).

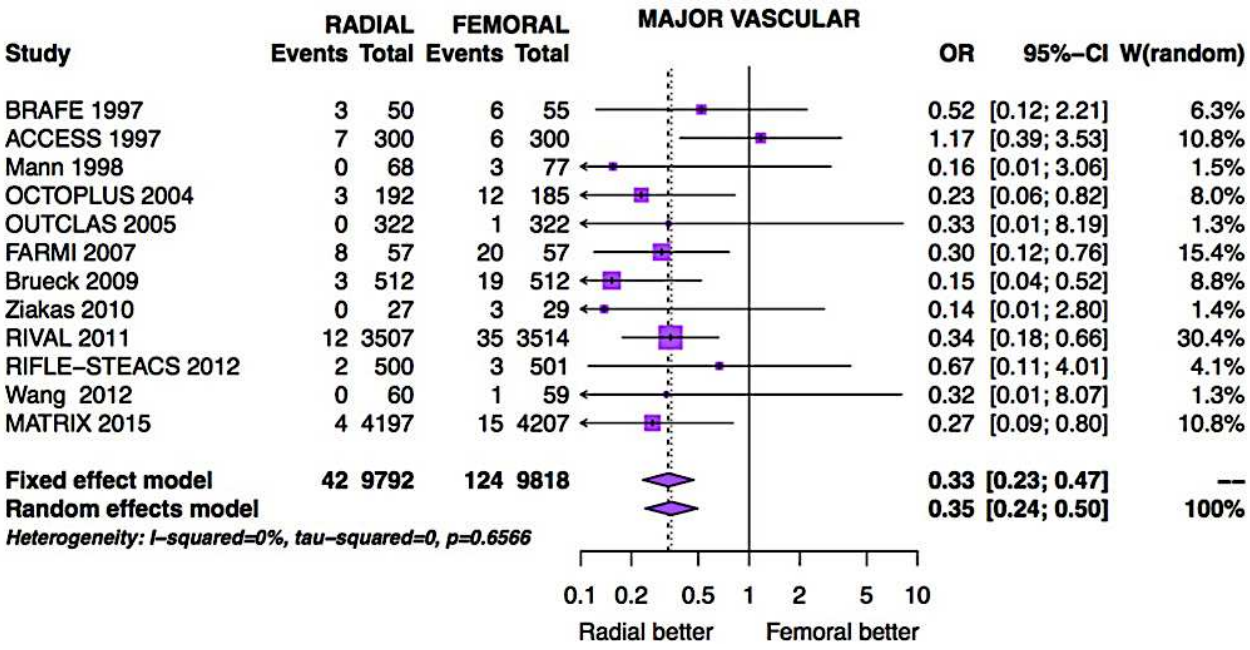

Figure 3. Rates of major vascular complications after TRA or TFA PCI in patients with either ACS or stable ischemic heart disease

Figure obtained from the work by Mason P, Shah B, Tamis-Holland J, Bittl J, Cohen M, Safirstein J et al. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. *Circulation: Cardiovascular Interventions*. 2018;11(12).

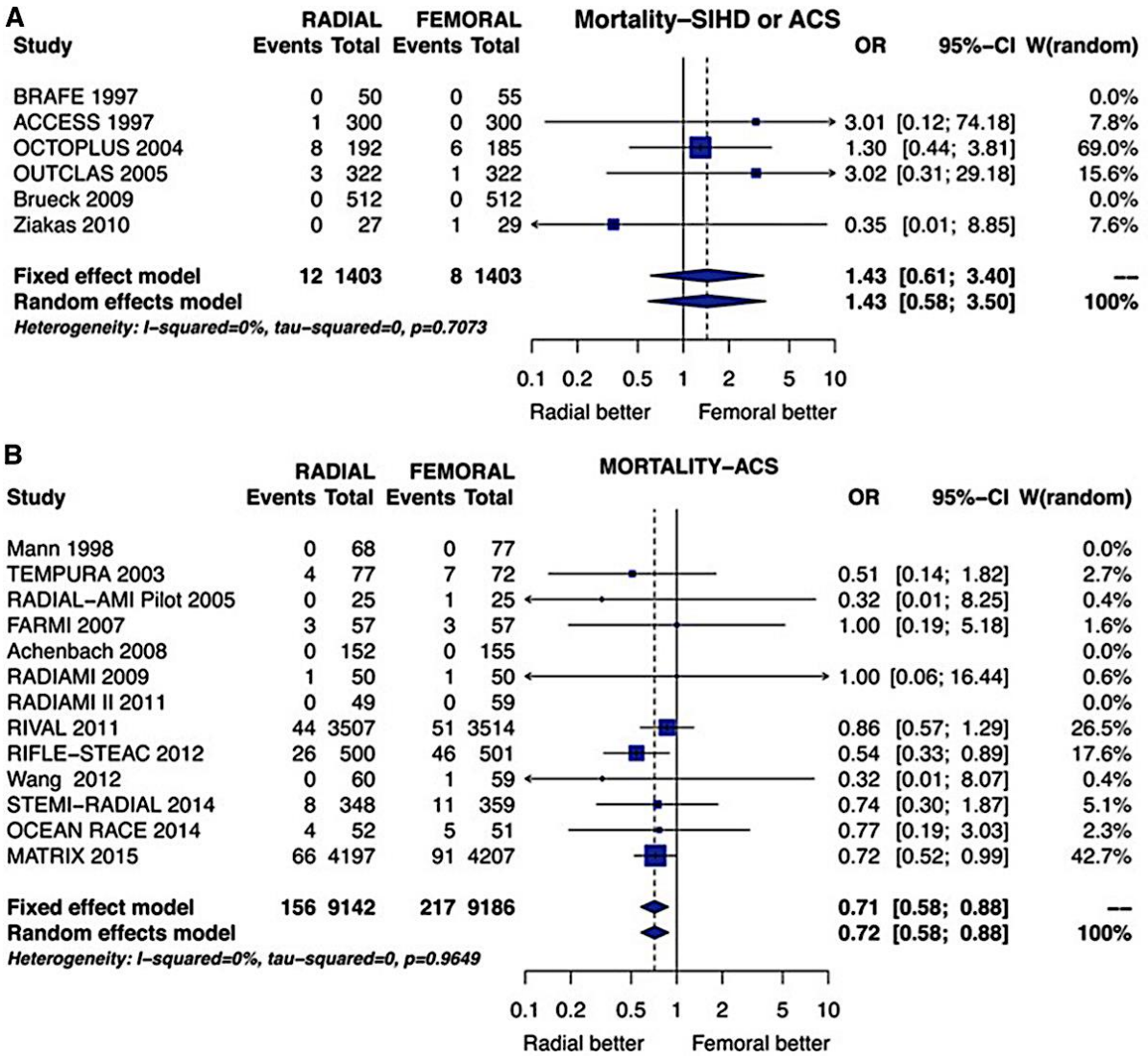

Figure 4. Rates of all cause mortality at 30 days or longest follow-up after TRA or TFA PCI in trials enrolling patients with (A) ACS or stable ischemic heart disease or (B) only ACS

Figure obtained from the work by Mason P, Shah B, Tamis-Holland J, Bittl J, Cohen M, Safirstein J et al. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. *Circulation: Cardiovascular Interventions*. 2018;11(12).

These results unequivocally show significantly reduced major bleeding rates after PCI being performed using TRA versus TFA, this both in trials enrolling only ACS patients (OR 0.60; 95% CI, 0.47-0.76) and in those including patients with either ACS or stable ischemic heart disease (OR 0.21; 95% CI, 0.08-0-52). The weighted bleeding rate in patients with ACS in patients undergoing TFA PCI was 5.5% whereas in TRA it was 3.4% (P<0.05).

Reduction in vascular complications is significantly more achieved among patients undergoing TRA PCI versus TFA PCI (OR 0.35; 95% CI, 0.24-0.50). The rate of weighted major vascular complications was 7.7% for TFA and 2.9% for TRA (P<0.05). In trials including both patients with ACS or stable ischemic heart disease, no significant difference in all-cause mortality between the two procedures was established. However, in the ACS-only group there was lower mortality after TRA PCI (OR 0.72; 95% CI 0.58-0.88) and the weighted mortality rate for TRA was 2.7% compared to 3.7% for TFA (P<0.05).

1.4. Procedural aspects of transradial vascular access

Although high-risk patient subsets including those with ACS exhibit the greatest relative benefits of TRA over TFA, maintaining an appropriate operator and center volume is crucial to achieving these advantages. Concerns with respect to access site crossing, exposure to radiation, volume of contrast, reperfusion time delay, and procedural success may be lessened with operator skill, according to analyses of the TRA learning curve (14, 20-23). In selecting patients it's important to consider certain characteristics. Short stature, female gender, increasing age (>75 years), and cardiogenic show are predictors of failure of TRA PCI (23,24). For patients with increased risk of bleeding, receiving oral anticoagulation or patients whom cannot receive blood transfusion, TRA may have particularly pronounced advantages (14, 25,26).

Preprocedural assessment of the radial pulse is of course important. Of historical interest is the Allen test, however it has been demonstrated that a normal or abnormal test previous to a TRA procedure did not produce a difference in grip strength, thumb capillary lactate, nor incidence of ischemia and it is largely abandoned from modern radial practice (1,27,28).

When selecting the site of access and setup of patient the most important goal is to perform a safe and successful PCI (14). The most preferred access site tends to be the right radial access, mainly due to comfort of the operator and limitations of catheterization laboratory equipment design (29). For right RA operations, it is advised to use a platform that offers transitional support for wires and catheters between the access site and procedure. In left RA operations, the operator's comfort can be increased by raising and retracting the patient's arm across the patient's body (14).

Access to the LRA through the dorsal side of the thumb in the anatomic snuffbox (**Figure 5**) is one alternative way reported, however the long-term safety implications of this procedure and its relevance to the ACS situation are unclear (14, 30). A recent study by Tsigkas

and colleagues showed that radial approach through anatomical snuffbox was feasible and safe for the purposes of interventional angiographic procedures and it was associated with reduced rates of radial artery occlusion as well as with less time required to reach hemostasis after procedure, compared to classical radial approach (31).

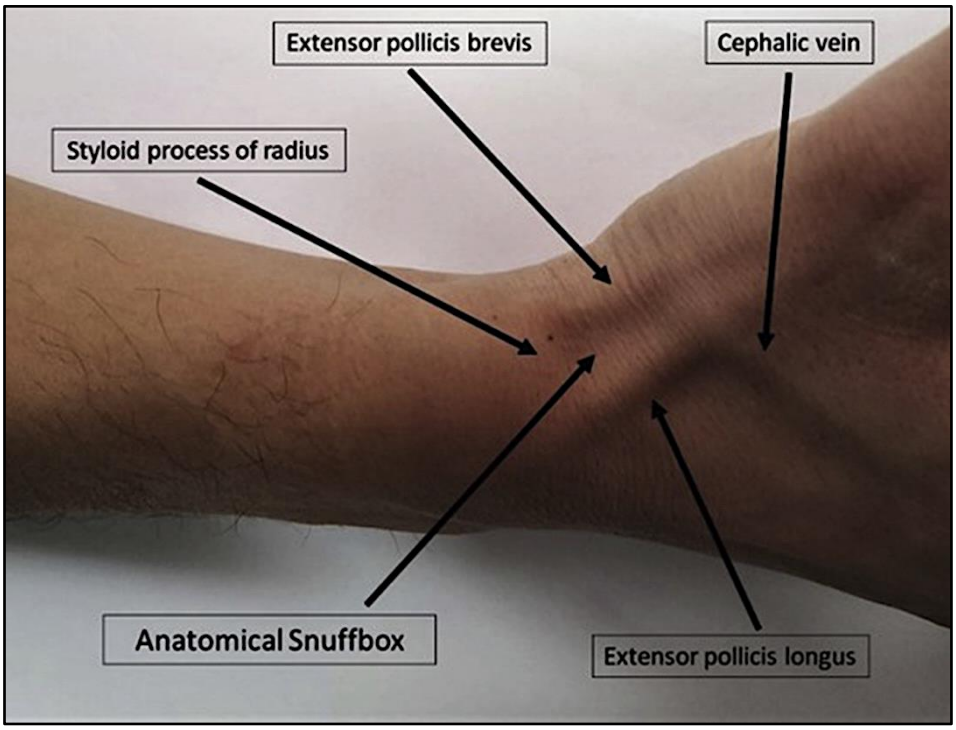

Figure 5. Anatomic characteristics of the snuffbox area where radial artery can be punctured

Figure obtained from work by Tsigkas G, Moulias A, Papageorgiou A, Ntouvas I, Grapsas N, Despotopoulos S, Apostolos A, Papanikolaou A, Smaili K, Vasilagkos G, Davlouros P, Hahalis G. Transradial access through the anatomical snuffbox: Results of a feasibility study. *Hellenic J Cardiol.* 2021 May-Jun;62(3):201-205.

Arterial access in TRA is enhanced with securely positioning the arm in a supinated, slightly hyperextended position at the wrist, while being parallel to the floor (14). Access can be achieved through either a single- or double- wall puncture technique. These are both effective and safe, with low association to vascular complications. There is however a higher first-pass success rate linked to the double-wall technique (14, 32). Further, guidance via ultrasonography can be useful, this especially in patients with hypotension, weak pulse or cardiogenic shock (14). Several studies have shown decreased amount of attempts and time to achieve access when using ultrasound for this purpose (33). In addition to access technique, other aspects increasing success rate include the use of specific dedicated radial sheaths that

has a hydrophilic-coating and tapered dilator. The use of these sheaths improve patient comfort and generate less radial artery spasm (RAS) (34,35).

The use of the smallest-caliber sheath achievable is encouraged to reduce radial artery occlusion (RAO) events. This “slender” approach however needs to be validated in larger clinical trials. Of notice, it has not been shown that sheath length affects the comfort of the patient, occurrence of RAS or RAO, nor the safety of the procedure (35).

1.5. Radial artery spasm

The most common but usually resolved complication encountered in cardiac catheterization through the radial artery is radial artery spasm. This results in discomfort for the patient and the success rate of the procedure is reduced (36). The smooth muscle cells that make up the radial artery's thick walls are organized in concentric layers. This artery is particularly prone to spasms due to its distinct muscular component and high density of alpha-1 receptors (36,37). It is a Type III artery, and compared to other somatic vessels, it has a higher sensitivity to spasm (38,39).

The advantages of using the radial artery as access site are diminshed when RAS occurs as it may also contribute to radial artery occlusion and injury (38). An example of radial artery spasm as visualized by contrast injection is provided in Figure 6.

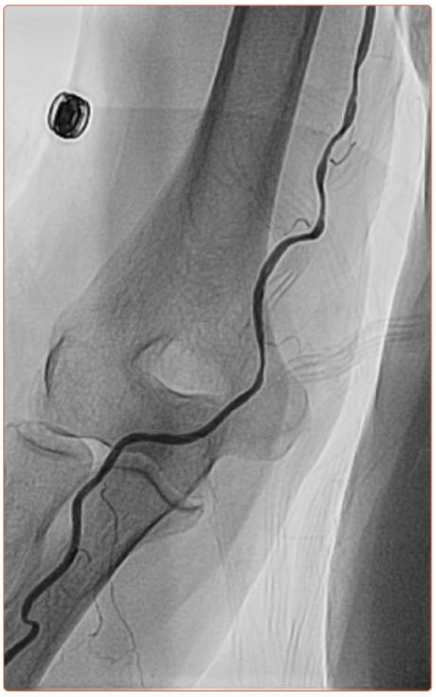

Figure 6. Angiographically verified radial artery spasm

Figure obtained from work by anawan Riangwiwat , James C Blankenship , Vascular Complications of Transradial Access for Cardiac Catheterization, *US Cardiology Review* 2021*;15:e04.*

The incidence of RAS was shown in a review to be up to 14.7%, however varies among studies, based on catheter or sheath type used, premedication applied, and criteria used (38). Perceived pain from patient and or problems in manipulation of the catheter or sheath removal were subjective RAS definitions used in some research works (39-45) whereas incidence of RAS in these studies differed in values between 6.8% to 30%.

A suggested criteria of an objective definition of RAS was introduced by Kiemeneij and colleagues - this proposal included a patient whom experienced pain and a maximum pullback force higher than 1.0 kg with sheath removal by an automatic pullback device. After this definition of RAS, 3 conducted trials reported an occurrence of radial spasm in 2 to 22% of cases, correlating with pain and a maximum pullback force of >1,0 kg (46-48).

Premedication with intra-arterial vasodilators is an important procedural step in RAS prevention (38). A review published by Kwok et al (49) compared the effect of several agents, including magnesium sulphate, nitroglycerin, isorobide mononitrate, nicorandil, verapamil, phentolamine, isosorbide dinitrate, nicardipine, and a combination of these. The RAS rate in placebo group was at 12%, which was the same for verapamil in a dose of 2,5 mg, however verapamil 5mg showed a RAS rate of 4%. The drugs showing the lowest RAS rate was isosobide mononitrate (4%), nicardipine (3%), and nitroglycerin both at 100mcg (4%) and 200 mcg (3%). Kristic et al (38) noted that a combination of verapamil in doses 1,5 to 5 mg and nitroglycerin 100 to 200 micrograms can reduce RAS rate to 3,8%. In this study it was also noted that RAS can further be decreased to 1% with the use of hydrophilic coated sheaths and catheters. Finally, gentle manipulation of the catheter, adequate use of spasmolytic agents and employment of hydrophilic catheters can significantly reduce the incidence of radial artery spasm.

1.6. General overview of topical and cutaneous analgesia before transradial angiography

Adequate analgesia seems to be important to prevent RAS, as the sensitivity of the radial artery to circulating neurohumoral factors is particularly high (38). Therefore, reducing pain and overall patient comfort is of interest in the field of transradial angiography. A protocol of local anesthesia that is already established as a gold standard is the subcutaneous infiltration of lidocaine with needle at the anatomical site where radial artery puncture is planned. This has shown to provide adequate local anesthesia for transradial coronary angiography peri-operatively (51). The dose and placement of administering subcutaneous lidocaine varies

slightly, from 0,5 to 0,7 mL of 1% lidocaine to 1 to 2 mL of 2% lidocaine. Placement varied from 0,5 to 1,5 cm proximally from the styloid process (50-54).

Topical analgesia prior to transradial angiography seems to be under growing interest, and is also at the central spot of this thesis. A known effective topical anesthetic agent is the EMLA cream, consisting of 2,5% prilocaine and 2,5% lidocaine solution. EMLA has been previously used for certain invasive procedures known to elicit pain, such as intravenous catheterization, arterial cannulation, phlebotomy and lumbar puncture (54). Application time varied between the studies from 30 minutes to 2 hours (50,51,53,54), however, in those reporting dosage, the standard adult dosage of 2.5 g was used. Beyer et al (55) evaluated the effect of a topical mixture consisting of 40 mg lidocaine and 30 mg nitroglycerin applied for at least 30 minutes before TRA. The study showed promising result on radial artery size, but did not examine pain outcomes. In a small single-centered study (56), a combination of 15% verapamil, 2% nitroglycerin and 5% lidocaine was applied as a topical formulation, showing reduced pain and increased radial artery size.

The goals of the present study were to determine if topical medication prior to radial artery cannulation will have impact on radial artery spasm, reduction in pain and mean number of cannulation attempts during cardiac catheterization.

2. OBJECTIVES

2.1. Aims of the study

The present thesis principally investigated whether the application of a topical cutaneous medication prior to radial artery puncture during the diagnostic coronary angiography will impact on the occurrence of radial artery spasm, pain experienced by the patient during the procedure, and mean attempts of radial artery cannulations. For this purpose, randomized controlled trials (RCTs) and prospective non-randomized placebo-controlled trials including patients undergoing elective diagnostic coronary angiography due to stable coronary artery disease (CAD) or suspected CAD were included. This thesis evaluated the following:

a) **Risk of radial artery spasm** during the procedure if topical cutaneous medications were used prior to radial artery puncture *vs.* traditional subcutaneous infiltration of lidocaine prior to vessel puncture
b) **Mean pain score**, as assessed by visual analog scale (VAS) obtained from the patient during the radial artery cannulation. Difference in mean pain score between two groups of interest were compared – patients receiving topical cutaneous medications prior to radial artery puncture *vs.* patients receiving traditional subcutaneous infiltration of lidocaine prior to vessel puncture
c) **Mean number of cannulation attempts** during the diagnostic catheterization procedure – this was directly compared between patients receiving topical medications *vs.* those receiving traditional subcutaneous infiltration of lidocaine prior to radial artery puncture

2.2. Hypotheses

Regarding the prespecified aims of the thesis, we proposed following hypotheses:

a) Risk of radial artery spasm will be significantly lower among patients receiving topical medications prior to radial artery cannulation *versus* those that did not receive topical medications but instead were randomized to subcutaneous infiltration of lidocaine
b) The mean pain score will be significantly lower in patients receiving topical medications prior to radial artery cannulation *versus* those that did not receive topical medications but instead were randomized to subcutaneous infiltration of lidocaine
c) The mean number of cannulation attempts will be significantly lower in patients receiving topical medications prior to radial artery cannulation *versus* those that did not receive topical medications but instead were randomized to subcutaneous infiltration of lidocaine

3. PATIENTS AND METHODS

3.1. Study design

This diploma thesis was designed as a cumulative meta-analysis of data derived from randomized controlled or prospective non-randomized placebo-controlled trials that investigated the use of topical cutaneous medications administered prior to radial artery cannulation preceding diagnostic coronary angiography in patients with stable or suspected CAD. The control allocated treatment consisted of standard-of-care procedure being the subcutaneous infiltration of lidocaine analgesia prior to radial artery cannulation.

The main objectives of this work were to examine whether the administration of topical medications prior to transradial catheterization procedure would be associated with a reduction of radial artery spasm occurrence, decreased level of pain perceived by the patient, and reduced number of vessel cannulation attempts. Due to the nature of this study, registration of a prespecified protocol and obtaining approval from Ethics Committee of University of Split School of Medicine were not required. The study was conducted under the sponsorship of the Department of Pathophysiology, University of Split School of Medicine (USSM).

3.2. Search strategy

The student mentor (JAB) developed the search strategy, while student (LF) and student mentor (JAB) independently carried out the search of electronic databases. Electronic databases that were included in the search encompassed National Library of Medicine (NLM) – PubMed, Ovid MEDLINE, Ovid Journals (full text), and SCOPUS. Search was conducted by using search terms: *„radial artery spasm“* AND *„coronary artery disease“* AND *„topical medication“* AND/OR *„cardiac catheterization“* AND/OR *“lidocaine”* AND/OR *“pain”* AND/OR *“coronary angiography”*. A manual search through these databases was performed to obtain full records of original randomized controlled trials that were designed to make head-to-head comparisons of topical medication application *vs.* anesthetic agent infiltration prior to radial artery cannulation for the purpose of diagnostic coronary angiography among patients referred due to stable or suspected CAD. Limitations of the search was made to records published in relevant peer-reviewed journals, with no year or time limit, in the English language. Furthermore, we only included randomized controlled studies or non-randomized prospective trials that involved adult human subjects. The date of the last database search was performed on July 5th, 2022. For the purpose of this analysis we did not perform grey literature search nor did we contact external authors to provide additional data or to obtain additional studies. Both the mentor (JAB) and student (LF) manually and independently performed the

literature search, screened available titles and abstracts for relevance, performed deletion of duplicate records and made a classification of obtained studies as *„excluded"* or in the need of further assessment or additional clarification. Such studies were labeled as *„potential for inclusion"* and were later scrutinized for potential inclusion in the analysis. Finally, we rigorously applied inclusion and exclusion criteria to all studies that were considered for potential inclusion. If a discrepancy was found or there was a disagreement concerning the search strategy between the two investigators, a joint discussion involving the opinion of the third independent expert with high expertise in research methodology resolved this (Associate professor JB at the Department of Pathophysiology, University of Split School of Medicine).

3.3. Selection and inclusion of studies based on predefined PICOS criteria

To be included in the meta-analysis, screened randomized controlled trials had to fulfill several inclusion criteria as laid out in the **PICOS** questions (**P**atient, problem, or population /**I**ntervention/**C**omparison/**O**utcomes/**S**tudy design), as follows:

1. **Patient population:** patients with suspected or established CAD/chronic coronary syndrome (CCS) scheduled to undergo diagnostic cardiac catheterization (coronary angiography) *via* transradial approach
2. **Intervention:** patients in the experimental arm received an intervention in the form of topical medication that was locally applied to radial artery puncture site and this solution consisted of local anesthetic or a combination of anesthetic and vasodilator agent.
3. **Comparison:** patients in the control arm were managed according to *standard-of-care* practice which entails the subcutaneous infiltration of the local anesthetic at the site where radial artery puncture is planned
4. **Outcome:** the outcomes of interest were risk of radial artery spasm compared between experimental arm (patients receiving topical medication) *vs.* control arm (patients receiving standard-of-care analgesia without topical medication) prior to radial artery puncture. Secondarily, we investigated whether the pain during the procedure, as perceived by the patient and quantified by visual analogue scale rating will be different between the two arms of interest and for these we calculated the mean difference in pain scores. Finally, the mean number of radial artery cannulation attempts was calculated for both intervention arms and then compared.

5. **Study design:** all studies had to be designed as randomized or prospective placebo-controlled trials in order to be considered for the potential inclusion in the analysis.

3.4. Exclusion criteria

Only studies that were designed as randomized controlled trials or prospective placebo-controlled studies comparing the use of topical medications with subcutaneous lidocaine infiltration prior to radial artery cannulation were considered for the inclusion.

In the following circumstances we excluded studies:

1. If the study had an observational (non-RCT) design or if it was not an original research article (*e.g.* a review, case report, etc.)
2. In the case the study did not report on any of the main outcomes of interest including radial artery spasm and/or pain during cannulation procedure and/or number of cannulation attempts. Furthermore, studies were discarded if they did not provide basic data on study length, study setting and location, and if they did not contain information on patient age, sex, comorbidity burden, baseline pharmacotherapies, etc.
3. If the study involved patients with acute myocardial infarction such as non-ST segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI) – potential studies performed in the acute setting were excluded
4. If the study involved minors (<18 years of age) or pediatric patients
5. If the study showed to be a duplicate report not providing additional or updated outcome data
6. Studies published in a language other than English

3.5. Data extraction

Data were manually extracted by the student (LF) and mentor (JAB) and were then inserted in prespecified sheets in Microsoft Excel.

3.6. Risk of bias assessment

Risk-of-bias 2 is the recommended tool to assess the risk of bias in randomized trials and it is structured to evaluate a fixed set of domains of bias. The risk of bias is inspected over five domains that critically evaluate potential biases arising from the randomization process

(D1), deviations from the intended intervention (D2), missing outcome data (D3), discrepancies in outcome measurements (D4), and selection bias (D5) with respect to reported results. Finally, the overall judgment for each study is provided rendering either low, high, or some concerns regarding the risk of bias.

Risk of Bias (RoB) (57) was assessed by using RoB 2 tool (revised tool for Risk of Bias in randomized trials), available on the following link: https://www.riskofbias.info/welcome/rob-2-0-tool

3.7. Statistical analysis (data synthesis)

Data analysis was performed by proposed Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (58).

For effect estimates on dichotomous outcomes (radial artery spasm – YES/NO), risk ratio (RR) with 95% confidence intervals (95% CI) was used as the main summary measure Mean difference analysis was performed in order to inspect potential differences in mean pain VAS score reported during cannulation and mean cannulation attempts. Fixed-effects model with Mantel-Haenszel statistical method was applied for analyses with low heterogeneity while random-effects model was applied for analyses that were marked by moderate or high heterogeneity. Meta-analysis was performed by using Review Manager software (RevMan, version 5.4, The Cochrane Collaboration, 2020).

Chi-square (χ^2) test of heterogeneity and Higgins I^2 statistic of non-consistency were used to assess heterogeneity across included studies. Studies with an I^2 statistic of 15% to <35% were considered to have low heterogeneity; >35% to 75% - moderate heterogeneity, and those with I^2 statistic >75% were considered as exhibiting high heterogeneity.

Publication bias was assessed by visually inspecting the obtained funnel plots and formal Egger's test calculation - P-values <0.05 indicated significant publication bias across included studies. All P-values reported were two-tailed and results were considered statistically significant if P <0.05 at all instances.

4. RESULTS

A total of 7 randomized trials and/or non-randomized prospective placebo-controlled studies were included in the final analysis.

The basic information about the studies including the total enrollment, studied period, study location, study type and if the study was multicentric or single-center are available in Table 2.

Table 2. Basic information about studies included in the meta-analysis

Authors of the study and year	Total number of patients	Study period	Study location	Multicentric or single-centre study	Study type
Joly et al. 1998	N=538	March 1994 to March 1996	Paris, France	Single-centre	Randomized controlled trial
Youn et al. 2011	N=76	September 2008 to March 2009	Yonsei University, Wonju, Korea	Single-centre	Randomized controlled trial Double blinded
Beyer et al. 2013	N=86	July 2010 - August 2012	University of California, San Francisco, USA	Single-centre	Randomized controlled trial Double blinded
Latsios et al. 2017	N=444	November 2014 – January 2018	"Hippokration" hospital, Athens, Greece	Multicentric	Non-randomized prospective placebo-controlled trial
Rigatelli et al. 2017	N=120	May 2015 to May 2017	Rovigo, Italy	Single-centre	Non-randomized prospective placebo-controlled trial
Tatli et al. 2017	N=104	December 2015 to May 2016	Sakarya University Hospital, Turkey	Single-centre	Randomized controlled trial
mikailiMirak et al. 2021	N=60	Undisclosed	Tehran, Iran	Single-centre	Randomized controlled trial Double-blinded

The baseline information on patients enrolled in the control arm with respect to baseline demographics, comorbidities, and pharmacotherapy provided in Table 3.

Similar information on patients in experimental arm is provided in Table 4.

Table 3. Age, sex, comorbidities, and baseline pharmacotherapy of of patients randomized to control arm

Authors of the study and year	**Mean age** (y) ± SD	**Male sex** N/N total (%)	**DM** N/N total (%)	**HTN** N/N total (%)	**DYSL** N/N total (%)	**Smoking** N/N total (%)	**Family history of CVD** N/N total (%)	**BB** N/N total (%)	**CCB** N/N total (%)	**Aspirin** N/N total (%)	**Nitrates** N/N total (%)
Joly et al. 1998	58 (44-72)	86	-	-	-	-	-	-	-	-	-
Youn et al. 2011	53 +/- 8	63,2	23,7	44,7	31,6	55,3	-	18,4	10,5	-	39,5
Beyer et al. 2013	59 +/- 12,8	65	21	74	67	23	-	65	14	69	9
Latsios et al. 2017	64,7 +/- 10,7	74,4	19,1	60,7	48,9	31,5	15,5	-	-	-	-
Rigatelli et al. 2017	69,2 +/- 7,5	78,3	65	68,3	48,3	74,9	-	-	-	-	-
Tatli et al. 2017	60,4 +/- 9,7	69,7	30,7	61,5	25	42,4	-	-	-	-	-
mikailiMirak et al. 2021	64,2 +/- 8,9	73,3	13,3	33,3	-	3,3	-	90	23,34	73,34	50

Abbreviations: BB-beta-blockers; **CCB**-calcium channel blockers; **CVD**-cardiovascular disease; **DM**-diabetes mellitus; **DYSL**-dyslipidemia; **HTN**-hypertension;

Table 4. Age, sex, comorbidities, and baseline pharmacotherapy of patients randomized to control arm

Authors of the study and year	**Mean age** (y) ± SD	**Male sex** N/N total (%)	**DM** N/N total (%)	**HTN** N/N total (%)	**DYSL** N/N total (%)	**Smoking** N/N total (%)	**Family history of CVD** N/N total (%)	**BB** N/N total (%)	**CCB** N/N total (%)	**Aspirin** N/N total (%)	**Nitrates** N/N total (%)
Joly et al. 1998	59 (45-72)	84	-	-	-	-	-	-	-	-	-
Youn et al. 2011	55,9 +/- 9	60,5	21,1	57,9	13,2	60,5	-	18,4	10,5	-	39,9
Beyer et al. 2013	63,4 +/- 12,6	67	26	68	67	12	-	62	7	74	5
Latsios et al. 2017	65,7 +/- 11,5	72	24	60	48,9	34,7	16	-	-	-	-
Rigatelli et al. 2017	68,5 +/- 8,8	68,3	56,6	80	40	86,6	-	-	-	-	-
Tatli et al. 2017	60,5 +/- 9,4	69,3	44,2	55,7	17,3	-	-	-	-	-	-
mikailiMirak et al. 2021	59,9 +/- 8,5	70	20	30	-	13,3	-	76,7	13,3	66,7	46,7

Abbreviations: BB-beta-blockers; **CCB**-calcium channel blockers; **CVD**-cardiovascular disease; **DM**-diabetes mellitus; **DYSL**-dyslipidemia; **HTN**-hypertension;

The allocation of treatments assigned to experimental and control arms and timing with respect to radial artery puncture during diagnostic cardiac catheterization as well as radial artery puncture technique are showed in Table 5.

Table 5. Treatment allocation across studies and procedural details

Authors of the study and year	Intervention treatment	Time of the application prior to procedure	Control treatment	Radial puncture technique and sheat size
Joy et al. 1998	EMLA cream (lidocaine + prilocaine)	2 hours	0.5-0.7 mL 2% lidocaine	18-gauge needle and 5F sheath
Youn et al. 2011	EMLA cream (lidocaine + prilocaine)	1 to 3 hours	0.6 mL 2% lidocaine	20-gauge needle and 5F sheath
Beyer et al. 2013	Topical Lidocaine (40mg) + Nitroglycerin (30mg) And 1% lidocaine sucutaneous	30 minutes	1 % lidocaine	6F sheath
Latsios et al. 2017	EMLA cream (lidocaine + prilocaine)	30 minutes	1-2 mL 2% lidocaine	20-gauge needle and 6F sheath
Rigatelli et al. 2017	EMLA (lidocaine + prilocaine)	30 minutes	2 mL 1% lidocaine	Seldinger technique and micropuncture
Tatli et al. 2017	Topical 5 % lidocaine And 1% lidocaine subcutaneous	30 minutes	1 mL 1% lidocaine	20-gauge needle and 5F sheath
mikailiMirak et al. 2021	Topical gel (5% lidocaine + 15% verapamil + 2% nitroglycerin	30 minutes to 3 hours	Placebo gel and 1% lidocaine subcutaneous	Not defined

4.1. Radial artery spasm

In the analysis of 1425 patients accumulated from seven RCTs, a total of 106 radial artery spasm events were recorded. The radial artery spasm occurred in 5.57% (40 events in 717 patients) of cases in the experimental arm while it occurred in 9.32% (66 events in 708 patients) of cases in the arm receiving standard treatment.

Patients receiving topical medication prior to radial artery cannulation exhibited a 41% relative risk reduction for the radial artery spasm (Figure 7), compared to patients receiving standard treatment (RR 0.59; 95% CI 0.41-0,86, *P*=0.005). This observation was based on the evidence of low degree of heterogeneity (I^2=7%).

No significant publication bias was detected (Figure 8).

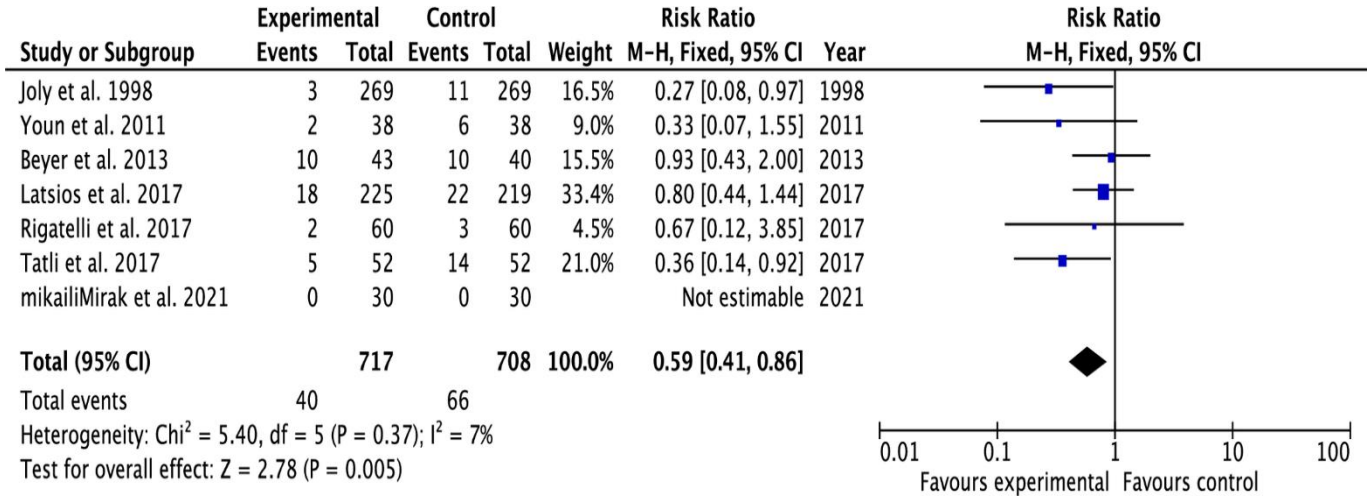

Figure 7. Relative risk of radial artery spasm with respect to treatment received prior to radial artery cannulation

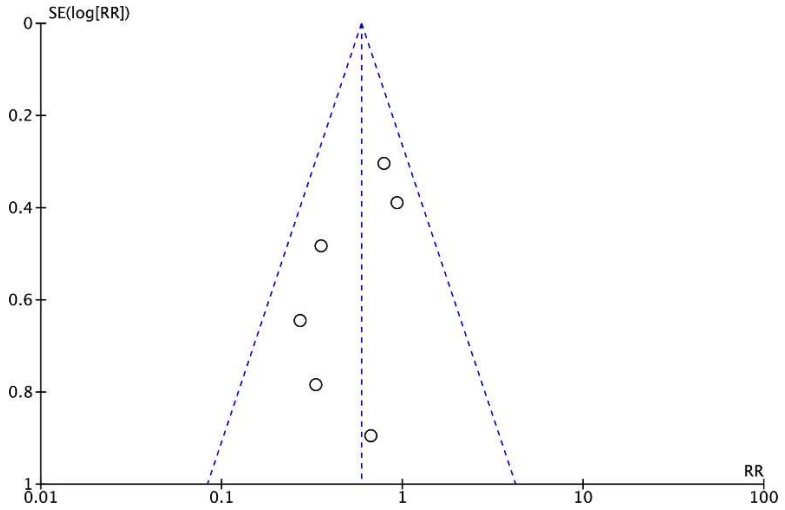

Figure 8. Publication bias across included studies for the outcome of radial artery spasm

4.2. Pain experienced during the radial artery cannulation

The pain was quantified by each patient by using visual analog scale (VAS), grading the pain from 0 (no pain) to 10 (maximum or severe pain).

This analysis included 6 studies that enrolled a total of 1342 patients. Analysis showed that application of topical medication prior to radial artery cannulation was accompanied by the significant 1.54-point reduction in perceived pain on VAS scale (MD -1.54; 95% CI -2.94 to -0.14 points, *P*=0.030), when compared to patients that received standard treatment (Figure 9). This observation was based on the evidence of high degree of heterogeneity (I^2=96%). No significant publication bias was detected (Figure 10).

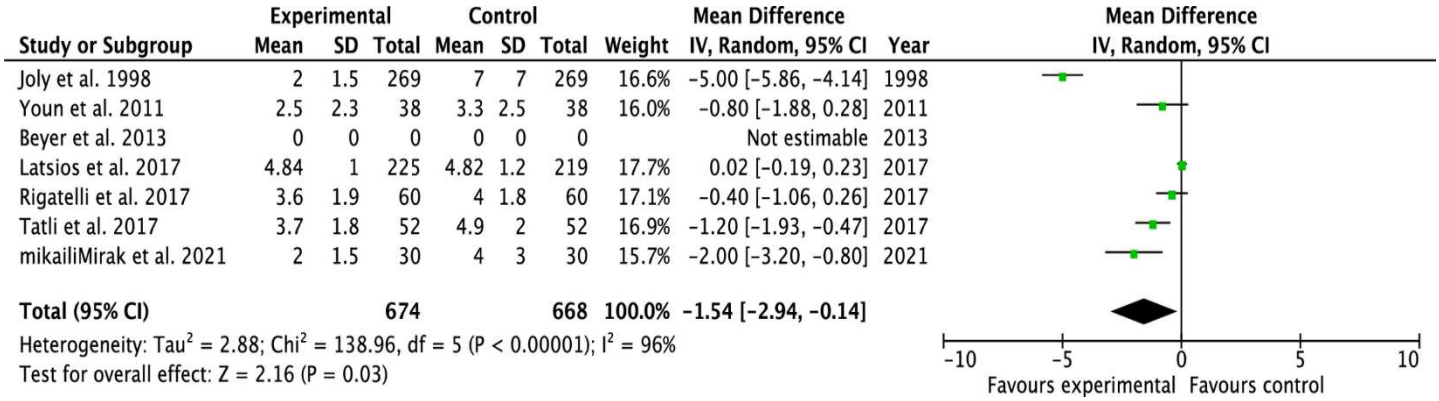

Figure 9. Mean difference in experienced pain as quantified by the VAS scale between two treatment arms, prior to radial artery cannulation

No significant publication bias was detected (Figure 10).

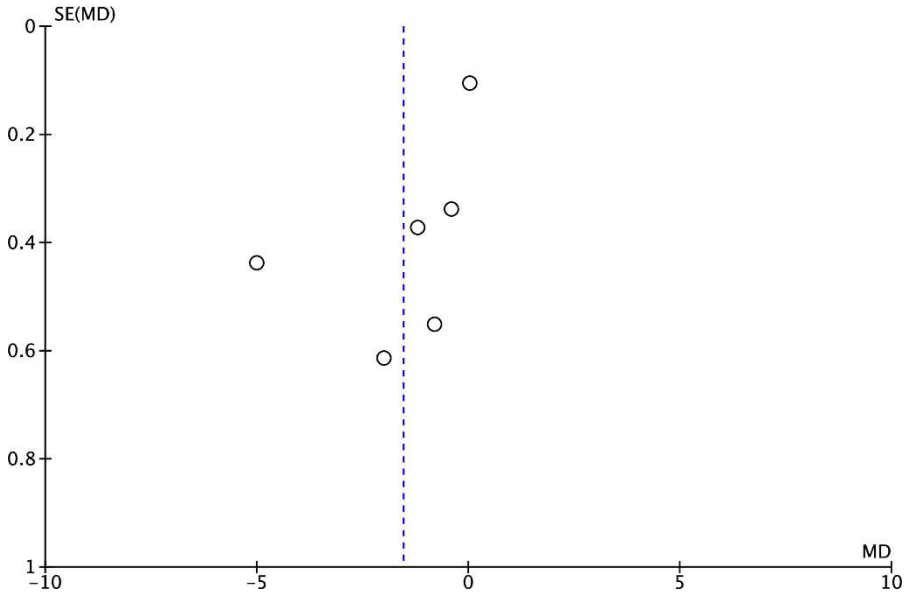

Figure 10. Publication bias across included studies for the outcome of mean pain score

4.3. Number of radial artery cannulation attempts

The mean number of radial artery cannulation attempts was recorded in four studies. This analysis included a total of 744 patients.

Analysis showed that application of topical medication prior to radial artery cannulation resulted in the -0.07 fewer cannulation attempts and this result was not significant (MD -0.07; 95% CI -0.14 to 0.01), however, this finding was not significant *(P*=0.070; Figure 11). This observation was based on the evidence of moderate degree of heterogeneity (I^2=54%).

No significant publication bias was detected (Figure 12).

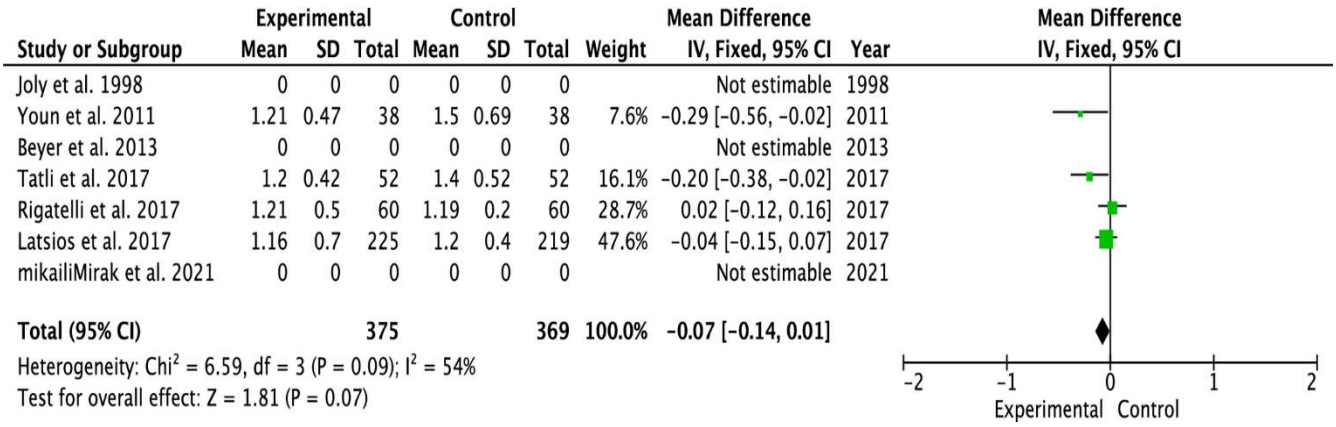

Figure 11. Mean difference in the number of radial artery cannulation attempts between two treatment arms

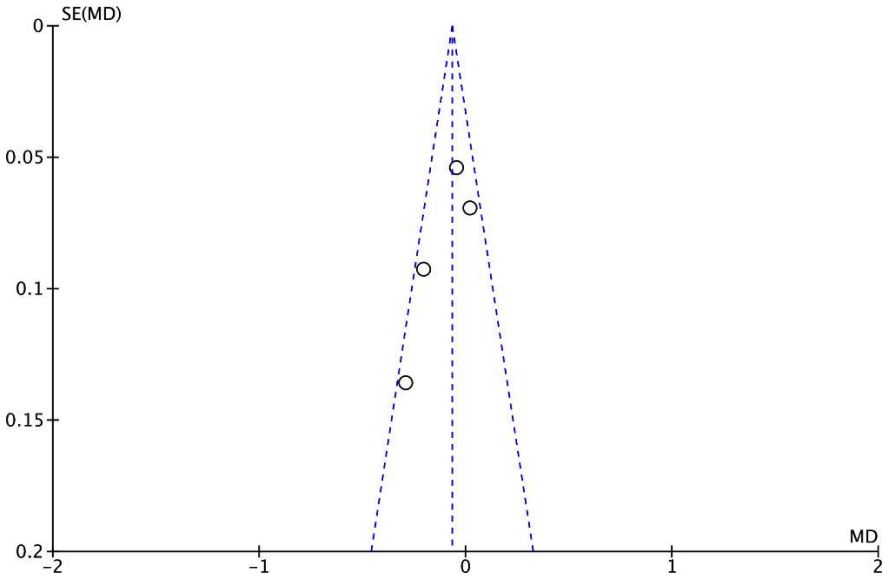

Figure 12. Publication bias across included studies for the outcome of mean radial artery cannulation attempts

4.4. Risk of bias (RoB) across included trials

Included trials had a heterogenous risk of bias with respect to randomization process with 4 trials having a low risk of bias in this domain, two having high risk of bias, and one trial yielding minor concerns with respect to this domain. Generally, included trials had a low risk of bias with respect to deviations from intended intervention, missing outcome data, outcome measurements and selection bias concerning reported results (Figure 13).

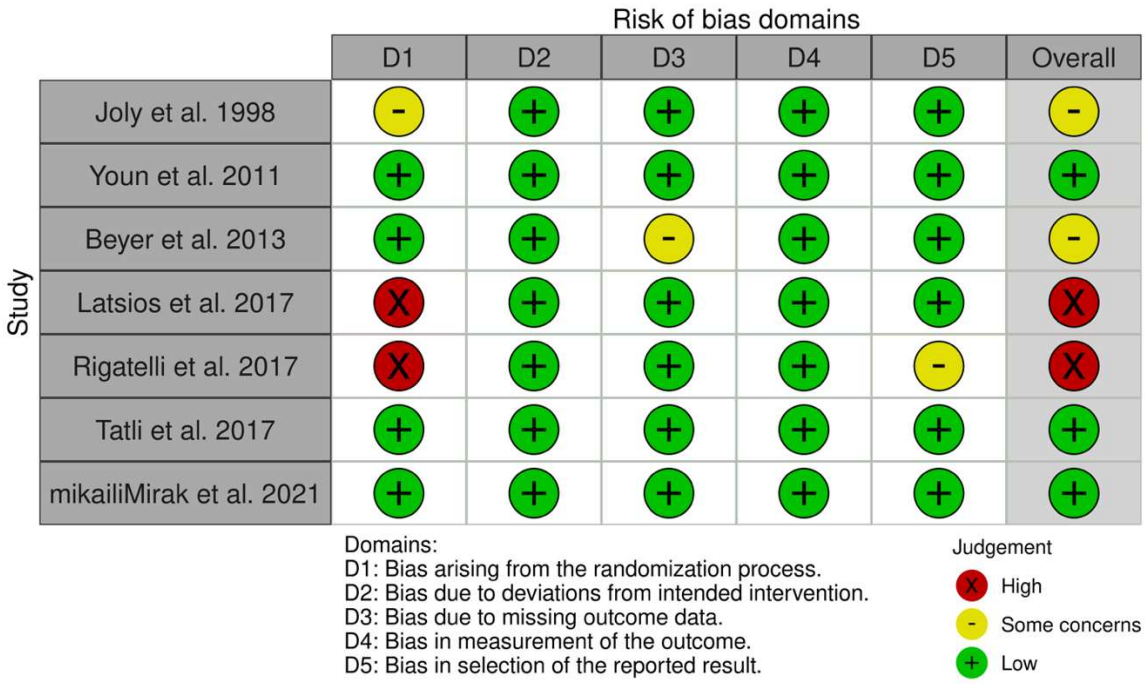

Figure 13. Risk of bias across trials (N=7) with respect to five bias domains

Overall risk of bias is shown in Figure 14**.** It can be appreciated from the figure that nearly half of included studies showed overall low risk of bias (Youn et al., Tatli et al., and mikailiMirak et al), two studies had some concerns regarding the risk of bias (Joly et al., Beyer et al.) while two studies were marked as having a high overall risk of bias (Latsios et al., Rigatelli et al.) due to high risk of bias in the randomization process domain.

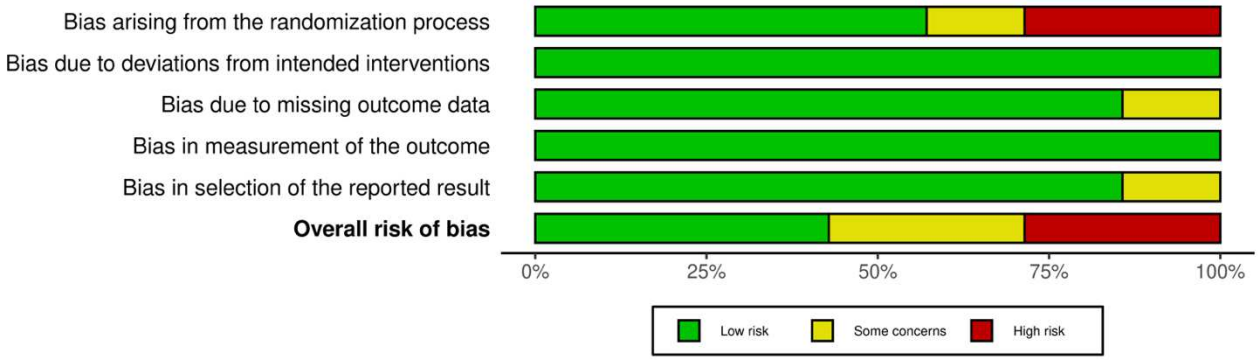

Figure 14. The overall risk of bias across included trials (N=7)

5. DISCUSSION

The results of this cumulative meta-analysis of randomized controlled trials or prospective non-randomized controlled trials showed that the application of topical medication prior to radial artery canulation preceding diagnostic angiography, compared to patients receiving standard subcutaneous infiltration of analgesics, was associated with a significant reduction of radial artery spasm and pain perceived by the patient.

This thesis presents the most up-to-date aggregation of data regarding this issue in interventional cardiology.

Thus far, only one systematic review examined the effect of topical medications on radial artery spasm in patients undergoing transradial coronary procedures (59). Curtis and colleagues examined three studies involving a total of 697 patients. In their study, authors found that patients in the experimental arm who were receiving eutectic mixture of local anesthetics had a likelihood of radial artery spasm reduced by 74% (OR 0.26; 95% CI 0.07-0.96), compared to patients receiving subcutaneous lidocaine. They also found that there were no significant differences in RAS in studies that compared eutectic combination of local anesthetics *vs*. placebo or combinations of lidocaine with nitroglycerine compared to placebo. In their systematic review, two included trials compared EMLA (mixture of prilocaine and lidocaine) to placebo and subcutaneous lidocaine while one study examined the use of topical lidocaine and nitroglycerin to placebo. Authors concluded that it is difficult to draw a definitive conclusion if the topical medications exert any favorable effect on radial artery spasm due to the low number of included studies, small sample size, and heterogeneity detected across trials.

There are some similarities and some notable differences between this previous work laid out by Curtis and colleagues and findings presented in this thesis. First of all, previous systematic review encompassed original studies published from 1989 to January of 2017 while in this thesis, three more studies that were published later in 2017 (50-52) were included with one additional study included that was published in 2021 (56). Two of these studies also investigated use of EMLA cream as the intervention, one investigated 5% topical lidocaine in conjunction with 1% subcutaneous lidocaine while one study investigated a unique topical gel that consisted of 5% lidocaine, 15% verapamil and 2% nitroglycerin. Secondly, for the purposes of this thesis, two non-randomized prospective placebo-controlled trials were included. Our analysis included a total of 1425 patients for the endpoint of radial artery spasm thus making our inferences more robust with demonstrated 41% relative risk reduction of radial spasm while this finding was based on the evidence of low heterogeneity.

Besides the mere update with respect to including more contemporary studies, this thesis also examined the endpoint of pain perceived by the patient during coronary angiography

which is an important factor from the patient's perspective, and it is a relevant patient-oriented outcome that is often neglected in clinical practice. Pain perceived by the patient during the angiographic procedure might precipitate radial spasm through neurohumoral feedback and activation of sympathetic pathways and catecholamine surge, therefore, efficient mitigation of periprocedural pain is likely to contribute to the successful closure of the procedure and would contribute to reduction in coronary artery access failure. However, more data on this are needed since there is a scarcity of studies investigating the relationship of the procedural pain perceived by the patient and procedural angiographic outcomes. The most prominent and important one was conducted by Ruiz-Salmeron and colleagues showing that independent predictors of radial artery spasm in multivariate regression analysis were radial artery anatomical anomalies yielding an odds ratio of 5.1, use of >size-3 catheters providing and odds ratio of 3.0 and moderate-to-severe pain during radial artery cannulation perceived by the patients with odds ratio of 2.6 (35). This same study showed that even up to 90% of patients that perceived radial artery cannulation pain as severe had in fact radial artery spasm occurring during the procedure. Such data illustrate that pain perceived by the patient during the radial artery cannulation is a valid endpoint to target since successful pain management will likely lead to less frequent radial artery occurrence.

The results of this thesis show that pain reduction with application of topical medications was consistent across included trials, and this resulted in more than 1,5-point reduction in pain severity as assessed by the patients on the VAS scale. However, the downside of this result is that it was obtained on data that was found to be of high heterogeneity and the 95% confidence intervals were wide. Therefore, such data characteristics might limit the generalizability of our findings. It has been demonstrated that application of cutaneous medications curbed perception of pain significantly which likely contributed to the lesser radial artery spasm occurrence.

Finally, the mean number of radial artery cannulation attempts did not significantly differ between patients receiving topical medications *vs.* standard subcutaneous lidocaine infiltration although patients that received topical medications had numerically lower mean number of cannulation attempts. This is likely due to lower number of included studies as only four studies reported on this outcome thus generating a sample size of 744 patients. This is a relevant endpoint since it has been previously demonstrated that the catheter size and increased number of attempts to cannulate radial artery likely imposes a higher degree of trauma on radial artery thus enhancing the risk of complications such as radial artery occlusion, dissection, spasm, pain, and pseudoaneurysm formation (60).

There are several limitations of this meta-analysis. First, not all of the studies were randomized controlled trials, since two studies were non-randomized prospective placebo-controlled studies. Secondly, there is a heterogeneity in intervention arm present since not all of the studies used same combination of compounds in the topical solution and some studies also differed in procedural aspects regarding the control arm. Thirdly, not all studies utilized the angiographic verification of radial artery spasm as the only objective identification of spasm thus introducing a heterogeneity in methods used to assess radial artery spasm and likely creating a bias with respect to adjudication of vasospasm episodes. Finally, it should be acknowledged that topical medication administration takes time to exert full analgesic and/or vasodilatory effect and it is required to be applied at least 30 minutes before planned cannulation. In this meta-analysis, most of topical medications were applied 30 minutes prior to procedure, however, some were applied even up to 3 hours prior to procedure. Therefore, it cannot be fully excluded that discrepancies in timing of administration of topical medications could impact on the outcomes that we report.

Finally, main findings of this thesis corroborate that the application of cutaneous topical medications likely reduces the incidence of radial artery spasm and pain perceived by the patient during cannulation for the purpose of diagnostic transradial angiography. However, the timing of this procedure remains the question as well as if the specific mixtures of compounds contained within the topical solution will yield differential results on patient-relevant outcomes as well as procedural success. Due to pharmacokinetic properties of these compounds, it is likely that their use will be confined to elective non-emergent settings such as among patients with stable CAD or stable patients with suspected CAD. Pharmacoeconomic aspect of using these solutions should also not be neglected as they would need to demonstrate their clear clinical advantage over current practices.

6. CONCLUSIONS

Based on the quantitative and meta-analytic synthesis of obtained data derived from 7 randomized controlled trials and prospective non-randomized placebo controlled trials examining the occurrence of RAS (radial artery spasm), mean pain score and mean number of cannulation attempts in patients with stable or suspected CAD undergoing diagnostic transradial coronary angiography, we can conclude the following:

1. The application of topical cutaneous medication prior to radial artery cannulation in patients with suspected or stable CAD had a significant risk reduction of 41% of radial artery spasm, compared to patients receiving standard-of-care treatment of subcutaneous lidocaine infiltration.
2. The application of topical cutaneous medication prior to radial artery cannulation in patients with suspected or stable CAD showed a significant reduction of 1,54 points (out of 10) in mean score of perceived pain on VAS scale, compared to patients receiving standard treatment of subcutaneous lidocaine infiltration.
3. The application of topical cutaneous medication prior to radial artery cannulation in patients with suspected or stable CAD resulted in -0,07 fewer cannulation attempts, however, this finding was not statistically significant.
4. Taken together, cutaneous application of topical medication compared to standard subcutaneous lidocaine infiltration prior to radial artery cannulation, in patients with stable or suspected CAD undergoing transradial angiography, significantly reduced the occurrence of radial artery spasm and was significantly less painful for the patient.
5. The described intervention, however, did not significantly reduce the number of radial artery cannulation attempts.

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8. SUMMARY

Objectives: The present study aimed to examine whether the application of a topical cutaneous medication, compared to standard subcutaneous lidocaine infiltration, prior to radial artery puncture in the setting of diagnostic coronary angiography will impact the occurrence of radial artery spasm, pain experienced by the patient during the procedure, and mean attempts of radial artery cannulation.

Patients and methods: Cumulative meta-analysis of data derived from 7 randomized controlled or prospective non-randomized placebo-controlled trials was performed. The primary outcomes of interest included relative risk of radial artery spasm during cannulation, mean pain score as perceived by the patient and quantified by visual analogue scale, and mean radial artery cannulation attempts. Risk ratio (RR) with 95% confidence intervals (95% CI) was used for the effect measurement of radial artery spasm while fixed effects method was applied. The mean difference was calculated by using the random effects model due to data exhibiting moderate to high heterogeneity. Meta-analysis was performed by using the Cochrane's Review Manager software.

Results: The data derived from seven studies enrolling a total of 1425 patients were included in the analysis. A total of 106 radial artery spasm events were recorded. Radial artery spasm occurred in 5.57% of cases in the experimental arm (topical solution), while in the arm receiving standard treatment radial vasospasm occurred in 9.32% of cases. This yielded a relative risk reduction of 41% in patients receiving topical medication (RR 0.59; 95% CI 0.41 to 0.86, P=0.005), compared to control arm. Analysis of 1342 patients from 6 studies in regards to pain quantified by VAS, the results showed a significant reduction in pain score by 1.54 points (MD -1.54; 95% CI -2.94 to -0.14 points, P=0.030) among patients that received topical medications *vs.* standard treatment. The mean number of radial artery cannulation attempts were recorded in 4 studies, including 744 patients. The results showed -0.07 fewer cannulation attempts in the experimental *vs.* control arm (MD -0.07, 95% CI -0.14 to 0.01), however, this result was not statistically significant (P=0.070).

Conclusions: Preprocedural application of topical cutaneous medication, compared to standard-of-care consisting of subcutaneous lidocaine infiltration, prior to radial artery cannulation in the setting of transradial angiography in patients with stable or suspected CAD was associated with a significant reduction in the occurrence of radial spasm and pain perceived by the patient. Application of topical cutaenous medication, however, did not reduce the mean number of radial artery cannulation attempts, when compared to subcutaneous lidocaine infiltration.

9. CROATIAN SUMMARY

Naslov rada: Utjecaj preproceduralne primjene topikalnih lijekova na dilataciju i učestalost vazospazma radijalne arterije u pacijenata koji se podvrgavaju transradijalnoj angiografiji

Ciljevi: Ova studija je kao glavni cilj imala istražiti je li primjena topikalnih lijekova koji se apliciraju na kožu, u usporedbi sa supkutanom infiltracijom lidokaina, a prije punkcije radijalne arterije za vrijeme dijagnostičke koronarne angiografije ima učinak na učestalost spazma radijalne arterije, bol koju pacijent osjeća za vrijeme kanulacije kao i prosječan broj pokušaja kanulacije radijalne arterije.

Pacijenti i metode: Izvršena je kumulativna meta-analiza podataka koji su sakupljeni iz 7 randomiziranih kliničkih pokusa ili nerandomiziranih prospektivnih placebom kontroliranih studija. Glavni ishodi od posebnog interesa su bili relativni rizik spazma radijalne arterije za vrijeme kanulacije, prosječan osjećaj boli koju pacijent osjeća za vrijeme radijalne kanulacije, a koji je kvantificiran korištenjem vizualno-analogne skale te prosječan broj kanulacija radijalne arterije. Omjer rizika (RR) sa 95% intervalima pouzdanosti je korišten kao mjera učinka ishoda spazma radijalne arterije, a za istu je korištena statistička metoda fiksnih učinaka. Razlika u prosječnom zbroju bola i pokušaja kanulacije je analizirana korištenjem statističke metode nasumičnih učinaka obzirom da su navedeni podatci pokazali umjerenu do visoku heterogenost. Meta-analiza je izvršena korištenjem Cochraneovog Review Manager programskog paketa.

Rezultati: Analizirani su ishodi 1,427 pacijenta iz sedam studija uključenih u analizu. Ukupno je zabilježeno 106 događaja spazma radijalne arterije. Spazam radijalne arterije zabilježen je u 5,57% slučajeva u grupi pacijenata koji su dobili topikalni lijek (eksperimentalna grupa) te u 9,32% slučajeva u grupi pacijenata koji su dobili standardnu skrb (kontrolna grupa). Navedena eksperimentalna intervencija bila je povezana sa smanjenjem relativnog rizika za spazam radijalne arterije za 41% (omjer rizika 0,59; 95%-tni interval pouzdanosti 0,41-0,86, *P*=0,005). Analizom ishoda boli prilikom kanulacije radijalne arterije kod 1,342 pacijenta iz 5 studija, pokazalo se da je intervencija topikalnim lijekom dovela do značajnog smanjenja boli za 1,54 boda u percepciji boli izmjerene VAS skalom u usporedbi sa pacijentima koji su dobili standardnu skrb (razlika u prosječnim vrijednostima -1,54 boda na VAS skali; 95%-tni interval pouzdanosti -2,94 do -0,14 bodova, *P*=0,030). Ishod prosječnog broja kanulacija radijalne arterije je analiziran u 744 pacijenta iz 4 studije. Za ovaj ishod nije utvrđena statistički značajna razlika između dvije skupine iako je u skupini pacijenata koji su primili topikalni lijek utvrđen trend smanjenja prosječnog broja pokušaja kanulacije radijalne arterije (razlika u prosječnim vrijednostima -0,07; 95%-tni interval pouzdanosti -0,14 do 0,01 pokušaja, *P*=0,070).

Zaključci: Aplikacija kutanog topikalnog lijeka prije kanulacije radijalne arterije, u usporedbi sa standardnom skrbi korištenja supkutane infiltracije lidokainom u pacijenata koji se podvrgavaju transradijalnoj angiografiji je bila povezana sa značajnim smanjenjem rizika radijalnog spazma kao i smanjenjem percipirane boli za vrijeme kanulacije radijalne arterije. Intervencija sa topikalnim lijekom, međutim, nije smanjila prosječan broj pokušaja kanulacije radijalne arterije u usporedbi sa supkutanom infiltracijom lidokaina.

10. CURRICULUM VITAE

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