THE EFFECT OF NITROGLYCERIN ON RADIAL ARTERY OCCLUSION AFTER TRANSRADIAL CATHETERIZATION : A SYSTEMATIC REVIEW

Cokorda Istri Padmi Suwari[1], Bayu Puradipa[2]
[1] Faculty of Medicine and Health Sciences Warmadewa University
[2] Faculty of Medicine Udayana University
E-mail : cokistripadmiswari@gmail.com

ABSTRACT

Background *: Transradial access is preferred approach for coronary angiography and PCI. Although, access site-related complications can occur following transradial access. RAO is the most common postprocedural complication. It has been reported that nitroglycerin can dilate radial artery in patients undergoing transradial coronary catheterization without affecting blood pressure.*

Objective: *This study aimed to evaluate the effect of nitroglycerin on RAO after transradial catheterization.*

Methods *: We searched RCT from Cochrane, PubMed, Science Direct, NCBI, and BMJ. Titles, abstracts, and full texts were screened using inclusion criteria to filter out irrelevant studies. Quality assessment were undertaken using Jadad scale and the results have been presented as a narrative overview with figures.*

Results *: Three studies were included after screening 206 records. Two studies demonstrated statistically significant results that giving nitroglycerin reduced the risk of RAO after transradial catheterization, compared with the comparator groups (p < 0.05). These studies were Chen Y et al 2018 (95% CI 0.116 - 0.998; p = 0.04) and Dharma S et al 2015 (OR : 0.62; 95% CI: 0.44 – 0.87; p = 0.006).*

Conclusions *: This study demonstrated benefit of using nitroglycerin for reducing incidence of RAO after transradial catheterization.*

Keywords : *nitroglycerin, radial artery occlusion, transradial catheterization*

ABSTRAK

Pendahuluan : Akses transradial adalah akses yang lebih dipilih untuk tindakan angiografi koroner dan IKP. Namun, komplikasi yang berhubungan dengan lokasi akses dapat terjadi. RAO adalah komplikasi pascaprosedural yang paling umum terjadi. Dilaporkan bahwa nitrogliserin dapat melebarkan arteri radial pada pasien yang menjalani kateterisasi koroner transradial tanpa mempengaruhi tekanan darah.

Tujuan: Penelitian ini bertujuan untuk mengevaluasi efek nitrogliserin pada RAO setelah kateterisasi transradial.

Metode : Uji RCT dikumpulkan dari Cochrane, PubMed, Science Direct, NCBI, dan BMJ. Kemudian judul, abstrak, dan teks lengkap ditelaah menggunakan kriteria inklusi untuk mengeksklusi studi yang tidak relevan. Penilaian kualitas studi menggunakan skala Jadad dan hasil penelitian disajikan dalam bentuk naratif yang dilengkapi dengan gambar.

Hasil: Tiga studi dimasukkan dalam penelitian ini setelah mengeksklusi 206 studi. Dua studi menunjukkan hasil yang signifikan secara statistik, yaitu pemberian nitrogliserin mengurangi risiko RAO setelah kateterisasi transradial dibandingkan dengan kelompok pembanding (p <0,05). Studi tersebut adalah Chen Y *et al* 2018 (95% CI 0,116 - 0,998; p = 0,04) dan Dharma S *et al* 2015 (OR : 0,62; 95% CI: 0,44 – 0,87; p = 0,006).

Simpulan : Penelitian ini menunjukkan manfaat penggunaan nitrogliserin untuk mengurangi kejadian RAO setelah kateterisasi transradial.

Kata kunci : nitrogliserin, oklusi arteri radial, kateterisasi transradial

BACKGROUND

Transradial access (TRA) is the preferred approach for coronary angiography and percutaneous coronary intervention (PCI) due to the reduced risk of bleeding, vascular complications, and requires shorter hospital stays as compared with transfemoral access (TFA). Transradial access has emerged as the predominant route for performing coronary angiography and PCI worldwide and class I recommendations for its use over TFA in patients with acute coronary syndrome in current European Society of Cardiology guidelines.[1,2]

Although TRA is associated with a lower likelihood of vascular complications compared with TFA, minor and major access site-related complications can occur following TRA. Radial artery occlusion (RAO) is the most common postprocedural complication, initially occuring at the puncture site.[1,2] Radial artery occlusion continues to be one of the limitations of transradial access and potentially limits the radial artery as an access site in the future. It has been reported that 2.8% to 11.7% of all patients undergoing transradial coronary catheterization develop RAO shortly after the procedure.[2,3]

Several strategies have been used to decrease the incidence of RAO including the use of anticoagulant, use of smaller sheath, maintanance of patency during hemostasis, or shortening the duration of compression.[3] Anticoagulant, vasodilators, and patent hemostasis are some measures available to reduce the risk of RAO. Vasodilators are often used to treat radial artery spasm after unsuccessful radial artey puncture, but there is also utility in prophylactically increasing the diameter of the radial artery to prevent RAO.[4]

It has been reported that local injection of nitroglycerin at the puncture site in patients undergoing transradial coronary catheterization can dilate the radial artery without affecting blood pressure. Nitroglycerin is a potent vasodilator and has been shown to deter radial artery spasm and act as a nitric oxide (NO) donor whereas NO has been demonstrated to inhibit vascular thrombosis and inflammation induced by transradial catheterizaton in pig model. In adults, nitroglycerin facilitates radial artery cannulation by increasing the internal diameter, shortening the procedure time, improving the success rate, and decreasing the incidence of radial arterial occlusion after cardiac catheterization.[2,5]

We hypothesized that nitroglycerin would decrease the incidence of radial artery occlusion after transradial catheterization. Thus, this study aimed to evaluate the effect of nitroglycerin on RAO after transradial catheterization.

METHOD

This study was designed as a systematic review which is started to define the research questions with PICO (population, intervention, comparison, outcomes) formula. Population of this study are patients undergoing transradial

catheterization who are indicated for diagnostic or therapeutic approach. As a intervention, patients received nitroglycerin before the catheterization procedure started or at the end of the procedure compare with placebo or other spasmolytic regimens. The primary study outcome was the incidence of RAO on the day following the procedure.

Studies were eligible for inclusion if : (1) paper are randomized controlled trial (RCT) (2) patients are greater than 18 yeats old (3) patients undergoing transradial chateterization who are indicated for diagnostic or therapeutic scheduled (4) patients received nitroglycerin before the catheterization procedure started or at the end of the procedure. Studies were excluded if : (1) abstract or full paper not available (2) paper are not using english (3) hemodynamic instability (4) nitrates intolerance.

Using Preferred Reporting Items for Systematic Review (PRISMA) guideline, we sought for relevant studies through electronic searches of Cochrane Central Register of Controlled Trials, British Medical Journal, Pubmed, NCBI, and Science Direct from 1995 through September 2021. We macthed the results derived after having used the following key words : “nitroglycerin” AND “transradial catheterization” AND “radial artery occlusion”. All studies retrieved from the databases were stored and checked for duplicates. All unique titles and abstacts were screened to identify relevant publications that met inclusion criteria by one reviewer. Full review was then applied to all studies available in full text for eligibility by 2 authors.

Paper selected for retrieval were assessed by 2 independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from Jadad Scale. Studies that score more than equal to 3 are classified as high quality design. Meanwhile, studies with a score less than 3 are classified as low quality design. There were no disagreements between the reviewers, negating the requirement for a third reviewer.

The search of literature, selection of studies, extraction of data, and quality assessment were initiated independently by 2 reviewer by using a standard approach. For each eligible study, we extracted and summarized data on study authors, year of publication, study design, study objectives, samples size, intervention, control group, and outcomes.

Due to the heterogeneity between the studies, a meta-analysis could not be undertaken, hence the results have been presented as a narrative overview with figures used to illustrate the data. The heterogeneity was due to types of medications used, dosage of medications and timing of the medication application

RESULT

A total of 206 records of RCT were identified from five databases. A total of 184 uniqe records remained after removal 22

duplicates. A total of 11 papers published until 2021 met our inclusion criteria were included for full-text review. After full-text review, a total of 3 articles were finally included in our systematic review **(Figure 1).**

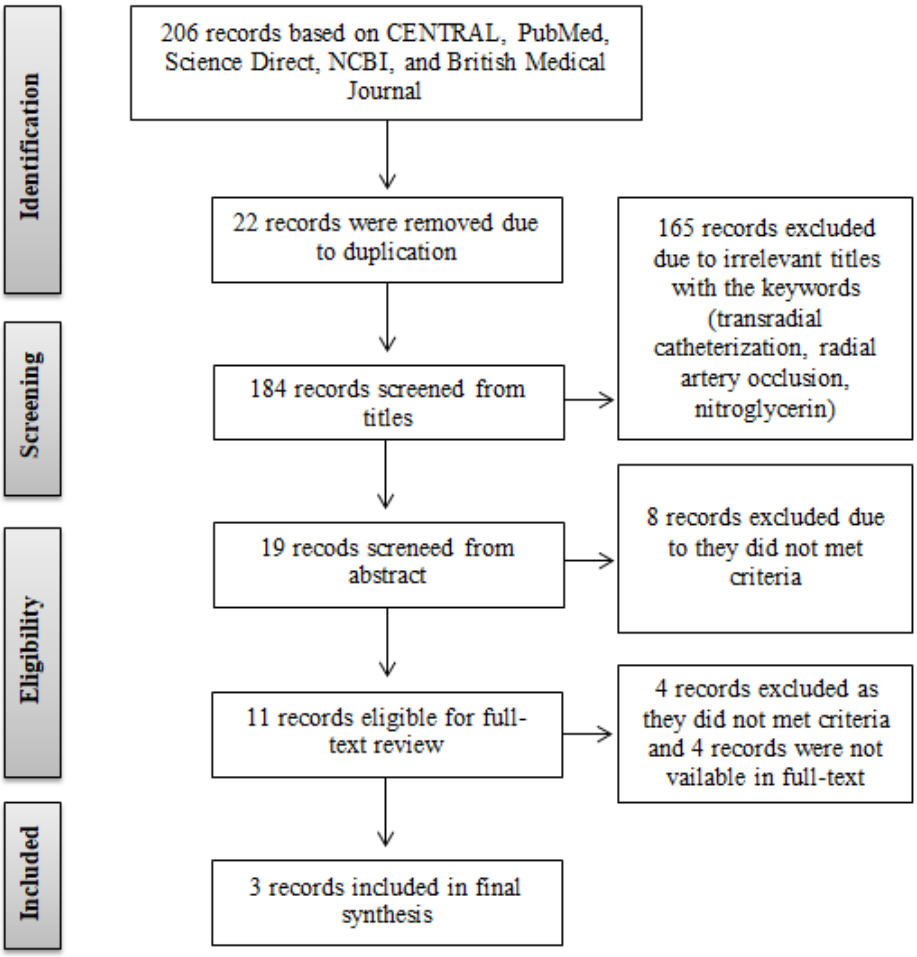

Figure 1. Search and selection proses based on PRISMA framework

Two independent reviewers carried out critical appraisal of the three papers using Jadad Scale checklist for randomized controlled trials. Papers were then scored based on the responses to the appraisal tool. A score of 5 was the highest possible score and would indicate a peper pf higher quality. Scores ranged from 3 – 5 and these papers were included despite high score **(Table 1).** In total, 206 papers were extracted from the literature from which 3 RCTs satisfied the eligibility criteria of this study. The characteristics of these 3 RCTs are summarized in **Table 2.**

Table 1. Critical appraisal results for selected studies

Author	Total score	Category
Dharma S et at 2018[6]	3	High quality design
Chen Y et al 2018[2]	4	High quality design
Dharma S et al 2014[3]	5	High quality design

Table 2. Characteristics of selected studies

Author	Intervention	Outcome
Dharma S et at 2018[6]	200 µg or 300 µg nitroglycerin intra-sheath after sheath placement	RAO occured in 16% of intervention group and 5.4% of control group. Neither use of verapamil nor nitroglycerin was associated with RAO (OR : 1.24 ; CI 95% : 0.51 – 3.02; p = 0.62)
Chen Y et al 2018[2]	500 µg nitroglycerin in 0.5 mL saline solution SC before procedure	The incidence of early RAO (within 24 hours) was substantially lower in the nitroglycerin treated group than in the placebo group (5.4% versus 14.4% ; CI 95%: 0.116 – 0.998; p = 0.04)
Dharma S et al 2014[3]	500 µg nitroglycerin intra-sheath at the end of the radial procedure	The use of nitroglycerin as compared with control , reduced the risk of RAO (8.3% versus 11.7%; OR : 0.62; CI 95% : 0.44 – 0.87; p = 0.006)

DISSCUSION

The radial access was first used in 1989. This approach showed real advantages with fewer bleeding and vascular complications, earlier mobilization and earlier discharge from hospital. But insertion of a radial sheath in the radial artery may be technically difficult because of small artery caliber, arterial vasospasm and low patient pain threshold.[7]

Radial artery occlusion is the most common complication of transradial interventions, with an estimated occurence of 2% - 10%. Although RAO is ussualy an asymtomatic complication, it can rarely cause serious hand ischemia.[8] Reported risk factors for RAO are inconsistent, but age, sex, body mass index, sheath-to-artery diameter, and procedure duration have been implicated as predictors of RAO.[4,9]

Radial artery size is an important determinant of the ease of radial artery access, the ability to use adequately sized sheaths and guide catheters and it potentially affects the rate of RAO. By enlarging the size of the radial artery, there are several potential benefits to the invasive cardiology community. First, the larger the artery, the easier it is to access percutaneously. Second, larger arteries facilitate the use of larger equipment. The small size of the radial artery has limited the use of larger equipment and this is one of the main disadvantages of the transradial

approach. Third, larger arteries are less likely to experience endothelial damage than small arteries, and thus may be less likely to spasm or become occluded. However this requires independent confirmation in future clinical studies.[10] Nitroglycerin has been noted to induce vasorelaxation and has been identified as effective in reducing spasm in the radial artery for coronary artery bypass grafting.[11]

We were able to include 3 randomized controlled trials including a total of 3.594 participants. This reviewed focused on 3 studies that investigated the use of varying dosages of nitroglycerin prior to transdial catheterization. There was significant diversity in the study population investigated. Out of the three trials reviewed, two were Asian European and one was Asian. The trials followed similar outcomes that measured the incidence of RAO. Two of three studies showed significant results that giving nitroglycerin reduced the risk of RAO after transradial catheterization. These studies were Chen Y et al (2018) and Dharma S et al (2015).

The trial conducted by Chen Y et al, showed that the incidence of early RAO (within 24 hours) was substantially lower in the nitroglycerin treated group than in the placebo group (5.4% versus 14.4%; p = 0.04). the relation risk for early RAO was 0.34 (95% confidence interval, 0.116 – 0.998) in the nitroglycerin-treated group as compared to the placebo group. Their study found that nitroglycerin injection at radial artery pucture site increases radial artery diameter is consistent with the notion that nitroglycerin acts as an NO donor.[12] Therefore, counteracting the reduction of NO release induced by radial artery puncture and mechanical friction between the sheath and the intima. The use of NO-coated sheath for transradial coronary intervention has been shwon to dilate vessel diameter at the access site immediately after percutaneous coronary intervention, decrease inflammation, reduce the risk of thrombosis, and inhibit intimal hyperplasia.[13] Because nitroglycerin acts as a NO donor, local injection of nitroglycerin may have a similar effect to the use of NO-coated sheath. The finding of Chen Y et al study that subcutaneous injection of nitroglycerin at the radial artery puncture site reduces early RAO, offers a cheaper method for reducing RAO incidence, and provides more directly and locally to the radial artery which will likely have less side effects.[2] In this study, nitroglycerin treatment did not cause hypotension, intolerable headache, or osteofascial compartement syndrome.

In the Dharma S et al trial, showed results that RAO on the day after the procedure as defined by doppler ultrasound was significantly lower in nitroglycerin group patients compared to placebo (8.3% versus 11.7%, p = 0.015). None of patients with RAO experienced any sign and symptom of hand ischemia nor requiring specific treatment at one day after the transradial procedure. The use of nitroglycerin reduced the incidence of RAO (OR = 0.62; 95%

confidence interval 0.44 – 0.87; p = 0.006). A mechanism where by nitroglycerin (nitrous oxide donor) may reduce the rate of RAO is thought to be through its vasodilatory effect of nitrous oxide. The dose of 500 µg nitroglycerin would have achieved a maximal vasodilatory effect and expected to decrease the intimal inflammation and intimal hyperplasia of the radial artery. This would be analogous to the findings from a nitric oxide-coated sheath that was shown to decrease intimal inflammation, intimal hyperplasia, and luminal thrombosis in a porcine model.[13] It is hypothesized that 500 µg of nitroglycerin would make a vasodilatation dominancy (through nitrous oxide) in the endothelium of the radial artery that would pharmacologically enhance flow, supporting a higher level of patency to preserve the radial artery during a hemostatis compression.[3]

Nitroglycerin is widely used in RA catheterization. Nitroglycerin is metabolised to release NO in smooth muscle, resulting in smooth muscle relaxation through activation of guanylate cyclase and increased cycluc guanosine monophosphate. The application of NO to the sheath used in RA approach might provide the local dilating effects of NO with the potential to avoid any unwanted systematic effects. The delivery of NO inhibit any platelet aggregation prompted by catheterization, preventing thrombosis during the procedure.[14]

Turan B et al (2015) compared pre-puncture SL (sublingual) nitroglycerin with conventional IA (intra-arterial) nitroglycerin after sheath insertion in transradial procedures. Fortunately, effect of SL nitroglycerin on safety endpoints was not different from IA nitroglycerin. The incidence of RAO, although not rare with 8.9%, was similar in both groups as well. In their opinion, relatively high incidence of RAO in their study was related to the use of 6 F sheaths and simple hemostasis technique. Incidence of nitroglycerin associated hypotension or bradycardia was very low and similar in two groups.[15] The comparison of nitrates suggests that when nitrates were compared to other nitrates there was no statistical significance.[16] Subcutaneous nitrates were shown to decrease radial artery spasm and facilitate radial artery cannulation after initial failed access attempt. Intra-arterial vasodilators reduce radial artery spasm and are now standard of care in transradial procedures.[17,18,19]

The heterogeneity of this study limits direct comparison of the studies. Due to the specific nature of our research question, our search yielded only three papers which limits the credibility of any conclusions drawn. Nevertheless, our review supports the administration nitroglycerin on reducing the incidence of RAO after transradial catheterization and this time window for introducing a nitroglycerin could potentially be further expanded.

Our study has some limitations. First, positive results are most likely to be

published and publications bias can not be completely excluded. Publication bias is another concern in systematic review as it might lead to false-positive overall conclusions. In fact, one of the major limitations of this systematic review is having reduced access to certain studies that we were not able to source as full text. Furthermore, some studies might still have been in publications process and not yet available to be sourced as full text and so could not be incorporated in this review. Second, such as small smple size in this study. Third, in addition, most studies captured by our systematic search came from a limited set of countries.

CONCLUSION

The evidence from this systematic review demonstrates a benefit in the use of nitroglycerin for reducing incidence of RAO after transradial catheterization. However, to determine more effectiveness of nitroglycerin, larger scale randomized control trials are needed.

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