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Intra-arterial vasodilators to prevent radial artery spasm: a systematic review and pooled analysis of clinical studies

Short running title: Vasodilators to prevent radial artery spasm

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Abstract

Objectives: The aim of this study is to review the available literature on the efficacy and safety of agents used for prevention of RAS.

Background: Different vasodilator agents have been used to prevent radial artery spasm (RAS) in patients undergoing transradial cardiac catheterization.

Methods: We included studies that evaluated any intra-arterial drug administered in the setting cardiac catheterization undertaken through the transradial access site (TRA). We also compared studies for secondary outcomes of major bleeding, procedure time, and procedure failure rate in setting of RAS prevention, patent hemostasis and radial artery occlusion.

Results: 22 clinical studies met the inclusion criteria. For placebo, RAS rate was 12% (4 studies, 638 participants), which was similar to 2.5 mg of verapamil 12% (3 studies, 768 participants) but greater than 5 mg of verapamil (4%, 2 studies, 497 participants). For nicorandil, there was a much higher RAS rate compared to placebo (16%, 3 studies, 447 participants). The lowest rates of RAS was found for nitroglycerin at both 100 µg (4%) and 200 µg (2%) doses, isosorbide mononitrate (4%) and nicardipine (3%). We found no information regarding the procedure failure rates, patent hemostasis, and radial artery occlusion in these studies.

Conclusions: In this largest and up-to-date review on intra-arterial vasodilators use to reduce RAS, we have found that the verapamil at a dose of 5 mg or verapamil in combination with nitroglycerine are the best combinations to reduce RAS.

Keywords: vasodilator; radial artery catheterization; radial artery spasm

Introduction

The radial artery is fast becoming the preferred access site for performing coronary angiography and percutaneous coronary intervention (PCI) [1]. In UK, adoption of the transradial access site (TRA) for PCI has increased from 10% in 2006 to over 60% in 2012 [2]. TRA is associated with reduced mortality and major adverse cardiac events (MACE) in selected cohorts at high risk of bleeding complications [2-4], thought to be related to a reduction in major access site related bleeding complications [1,5]. Transradial access is also associated with improved patient comfort and has also shown to be the preferred access site amongst patients undergoing PCI and be more cost effective than transfemoral access [6-8].

However, TRA approach is not without limitations, it is associated with a longer learning curve and complex procedures requiring large bore guide catheters are not always possible particularly in patients with small diameter radial arteries. Furthermore operators may encounter radial artery spasm (RAS) [9] during TRA particularly at the beginning of the learning curve, or when encountering radial anomalies. A previous review of 19 papers with 7,197 participants found that the incidence of RAS was 14.7% in patients in whom the radial artery was chosen as the access site for coronary angiography or PCI [10].

RAS leads to patient discomfort, increased risk of vascular complications and procedure failure rate. Various drugs such as nitroglycerin, verapamil, isosorbide mononitrate are used to reduced the risk of RAS. However, there is high variability in practice amongst operators for administration of these drugs. Furthermore, there are no guidelines or recommendations for using such drugs in day-to-day practice. Therefore, we conducted a systematic review of the available literature to evaluate the efficacy of agents used for prevention of RAS.

Methods

We searched MEDLINE and EMBASE on October 2014 using the broad search terms: "vasodilator" AND "radial artery occlusion" OR "radial artery spasm" OR "transradial." The search results were reviewed by two independent judicators (CSK, MR) for studies that met the inclusion criteria and relevant reviews. The bibliographies of included studies and relevant reviewers were screened for additional studies.

We included studies that evaluated any intra-arterial drug administered in the setting of TRA. The inclusion criteria was

1. Studies had to compare more than one agent or include a control group. There was no restriction based on sample size.
2. The studies had to evaluate some form of measure related to RAS such as incidence of RAS, change in diameter of radial artery and any adverse events associate with intra-arterial drug administration.

We excluded studies that administered drugs that were not intra-arterial and in-vitro studies.

Data was extracted from each study into preformatted spreadsheets. The data collected was on the year, country, number of participants, age of participants, % of male participants, participant inclusion criteria, and type of treatments, efficacy outcomes and safety outcomes. These results were narratively synthesized and trials with similar treatment arms were pooled using methods previous described [11].

We also compared studies for secondary outcomes of procedure time, and procedure failure rate in setting of RAS prevention and radial artery occlusion.

Results

Our search yielded 123 relevant articles and after screening and reviewing full manuscripts, 21 articles met the inclusion criteria with 22 clinical studies [12-32]. The process of study selection is shown in Figure 1.

The study design and participant characteristics of the included trials is shown in Table 1. Majority of studies (n=14) used blinding and these studies took place between 1997-2007 in different centers around the world. There were a total of 8,777 participants (range of participants in each study 30 to 1,950) with an average age of 61 years and 70% were male participants. All studies took place in the setting of transradial access (TRA).

Table 2 shows the different treatments that have been used as intra-arterial vasodilators and results from the studies. Many agents were evaluated including verapamil, magnesium sulphate, nitroglycerin, nicorandil, diltiazem, isorobide mononitrate, petolamine, isosorbide dinitrate, molsidomine, nicardipine, placebo and combinations of these drugs as well as other drugs such as nitroprusside. A variety of outcomes evaluated included any measure of changes in radial diameter, RAS rates, procedural success, blood pressure changes and radial occlusions and semi-occlusions.

Radial artery spasm was the most frequently evaluated outcome, which was evaluated for the efficacy of individual drugs in 14 studies (Table 3). For placebo, RAS rate was 12% (4 studies, 638 participants), which was similar to 2.5 mg of verapamil 12% (3 studies, 768 participants) but greater than 5 mg of verapamil (4%, 2 studies, 497 participants). For nicorandil, there was a much higher RAS rate compared to placebo (16%, 3 studies, 447 participants). The lowest rates of RAS was found for nitroglycerin at both 100 µg (4%) and 200 µg (2%) doses, isosorbide mononitrate (4%) and nicardipine (3%).

Combinations of different drugs were also evaluated in several studies[15,16,18-20] combining agents offered no advantage. The best studied combination of verapamil and

nitroglycerin was evaluated in 5 studies [16,17,22-24]. The pooled results of these studies yielded 21% RAS rate (5 studies, 135/630) however, two studies[17,23] reported unusually high rates of RAS (71% and 52% respectively) and differed from the other studies because the verapamil dose was low (100 µg). Excluding these studies the pooled rate of RAS for the verapamil/nitroglycerin combination was 9% (3 studies, 45/483).

Other outcomes

Several studies evaluate outcomes other than RAS. Abe et al found that ISDN was most potent vasodilator compared to verapamil, lignocaine and placebo [12]. While this study examined multiple doses, it was underpowered across each group. Boyer et al found that a combination of nitroglycerin and verapamil was associated with greater vasodilation compared to placebo [13]. Byrne et al found that magnesium is a more potent vasodilator than verapamil [14]. Carrillo et al found similar vasodilation with nitroglycerin/verapamil and verapamil alone [15]. Dalal et al found similar decreases in radial artery diameter with nicorandil compared to nitroglycerin/diltizem but there is less blood pressure drop with nicorandil [19]. Dharma et al found similar rates of procedural success with nitroglycerin with and without diltiazem [20]. Sekai et al found greater vasodilation with nitroglycerine compared to ISDN and verapamil [29]. In addition, the adverse events reported in each included study are presented in Table 5.

We also analysed these studies for procedure failure rate i.e. switching from TRA to TRF, procedure duration, catheter information and radial artery occlusion, Table 4. Only four studies compared procedure duration out of which two studies showed it was non-significant in both treatment and placebo arms, Byrne et al reported increased procedure duration in treatment arm.

No information was available regarding the procedure failure rates and radial artery occlusion in these studies.

Discussion

In this largest and up-to-date review on intra-arterial vasodilators to reduce RAS, we have found that many agents have been evaluated as potential vasodilators to reduce RAS. We found that the pooled rate of RAS in the placebo arm of several studies was 12% and only 5 mg of verapamil had lower pooled rates of RAS (4%). There were many single studies that evaluated the efficacy of different agents but many of these were underpowered. Nitroglycerin appears to reduce RAS but other less studied agents such as ISMN and nicardipine require further investigations. Several different cocktails or combinations of drugs have been tried and the best combination is nitroglycerine and verapamil which lead to 9% RAS if administered at adequate doses. For other cocktails of medications, there is inconsistent evidence that one combination is superior to another.

Several previous reviews have evaluated RAS during transradial procedures. The review by Ho et al reported that the incidence of RAS was 4 to 20%, which is consistent with the findings of 12% in the pooled results of the placebo arm of the current study [33]. The Ho et al review also discusses RAS prevention strategies including the use of pharmacological agents including intra-arterial vasodilatory cocktails but caution the use of verapamil because it is contraindicated in severe left ventricular function and bradycardia [33]. Another review by Kristic et al pooled the results from 19 studies had reported that the incidence of RAS was 14.7% which is slightly higher than the current study [10]. The review by Kristic et al recommended that the combination of verapamil (1.25-5 mg) and nitroglycerin (100-200 µg) can reduce RAS by up to 3.8% [10]. This combination is also supported by another review [34]. Our study supports the use of this combination of drugs at the recommended doses, as rate of RAS was 9% using this regime in the current study.

The advantages and disadvantages of vasodilatory agents in preventing RAS has been previous reviewed [35]. Nitroglycerine or glycerine tri-nitrate promote smooth muscle relaxation and hence vasodilation but there are risks of tachyphylaxis, withdrawal and hypotension. Verapamil is negatively inotropic and less effective than nifedipine but nifedipine is only available orally. Nicardipine is a strong calcium antagonist while diltiazem is negatively inotropic, less potent and has a slow onset. Nicorandil is less negatively inotropic compared to calcium channel antagonists. While there is no clear agreement on the optimal agent, verapamil-glyceryl trinitrate may represents the optimal combination [35].

While our study has shown that many intra-arterial agents can be used to prevent radial artery spasm, the use of sublingual agents in intractable cases of radial spasm is unclear. There is a study by Al-Waili et al which found that sublingual verapamil and nifedipine may lower blood pressure in hypertensive patients and it may be possible that these agents could be used to reduce radial spasm [36]. It may be possible for use of sublingual nifedipine in cases of intractable radial artery spasm in hypertensive patients but more studies are needed.

Our study has several strengths and limitations. This is the largest review with 22 clinical trials with data from 8,777 participants. We were able to pool the results for risk of RAS across many studies and found that the most effective agents appear to be verapamil alone or nitroglycerine and verapamil combination.

Our study is limited by the quality of the evidence available in literature. There are several studies that are significantly underpowered. There were as low as 30 patients in one study [15] and has low as 10 patients in each arm in another study [12]. Furthermore, many of the included studies were not fully published and were only available in abstract form. While, these studies may have limited information inclusion of these studies reduces publication bias. Furthermore, many of these studies were derived from well over a decade

ago and so the rates of 12% RAS reported in the placebo arms seem high in comparison to those encountered in daily practice by the authors of the manuscript. This may relate to the lack of radial specific equipment and sheaths used in these studies that would increase RAS rates, particularly when using sheaths without hydrophilic coatings [37]. An additional factor is that many centers use smaller diameter 5Fr radial sheaths and catheters for diagnostic cardiac catheterization that would decrease rates of RAS observed as would use of more contemporary thinner wall sheaths such as the Glidesheath Slender which combines an inner diameter compatible with 6Fr guiding catheter with an outer diameter close to current 5Fr sheaths where RAS rates have been reported as low as 4.4% [38]. Finally sheathless guide catheter usage may also result in lower rates of RAS than those reported in the 'placebo' control arm with previous data reporting RAS rates of 5% [39].

No data were available about radial spasm and radial artery occlusion in these studies in the setting of pharmacological prevention of RAS. Previous studies have suggested that RAS may increase the risk of radial artery occlusion, for example Rathore et al observed a high incidence of radial occlusion in patients with documented RAS in their randomized study investigating the influence of sheath coating and length on RAS rates (14.5% vs. 7.4%, $p = 0.003$) [37].

Minimizing RAS either pharmacologically or via sheath/catheter selection certainly increases procedure success rate, reduces procedure duration and hence radiation exposure and minimizes the short and long term radial vascular complications. Our review highlights the gap in literature on these important outcomes in setting of reducing RAS pharmacologically and further studies are required to study this.

Conclusion

In this largest and up-to-date review on intra-arterial vasodilators use to reduce RAS, we have found that the verapamil at a dose of 5 mg or verapamil in combination with nitroglycerine are the best combinations to reduce RAS. The use of other agents to prevent RAS such as nicardipine, ISMN and magnesium requires more studies. Operators should consider optimal sheath and catheter selection, as well as pharmacological regime to minimize RAS particularly in procedures undertaken in patients at increased risk for RAS such as females, the elderly and those with small diameter radial artery sizes.

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Table 1: Study design and participant characteristics of studies which evaluated intra-arterial vasodilators.

Study ID	Design	Year	Country	No. of participants	Mean age	% male	Participants
Abe 2000 [12]	RCT	1997	Japan	100	64	64	Transradial catheterization.
Boyer 2013 [13]	Blinded RCT	NR	USA	121	61	65	Transradial catheterization.
Byrne 2008 [14]	Double blind RCT	2007	Researchers from Canada and UK.	86	NR	NR	Transradial catheterization.
Carrilo 2011 [15]	Double blind RCT	NR	Spain	30	63	77	Transradial catheterization.
Chen 2006 [16]	Blinded RCT	2002-2003	Taiwan	361	64	68	Transradial catheterization.
Cho 2008 [17]	RCT	2007	Korea	142	64	74	Transradial catheterization.
Coppola 2006 [18]	Double blind RCT	NR	NR	379	57	83	Transradial catheterization.
Dalal 2011 [19]	Single blind trial	NR	India	200	NR	NR	Transradial catheterization.
Dharma 2012 [20]	Double blind RCT	NR	Indonesia	150	58	72	Transradial catheterization.
Hizoh 2014 [21]	Double blind RCT	NR	Hungary	591	62	64	Transradial catheterization.
Kiemeneij 2003 [22]	Non-randomized, non-blinded trial	NR	Netherlands	100	64	75	Transradial catheterization.
Kim 2007 [23]	Double blind RCT	2005	Korea	150	60	53	Transradial catheterization.
Manickam 2011 [24]	Non-randomized, non-blinded trial	NR	India	600	NR	NR	Transradial catheterization.
Mont'AlverneFino 2003 [25]	Double blind RCT	2000-2001	Brazil	51	56	74	Transradial catheterization.
Rosencher 2012 [26]	Double blind RCT	NR	France	332	NR	NR	Transradial catheterization.
Rosencher 2013 SPASM 3 [27]	RCT	NR	France	731	NR	NR	Transradial catheterization.
Ruiz-Salmeron 2005 [28]	Double blind RCT	2003-2004	Spain	500	63	76	Transradial catheterization.
Sakai 1999 [29]	Non-randomized, non-blinded trial	NR	Japan	186	NR	NR	Transradial catheterization.

Varenne 2006 SPASM 1 [30]	Double blind RCT	2003	France	1219	60	75	Transradial catheterization.
Varenne 2006 SPASM 2 [30]	Double blind RCT	2004-2005	France	618	62	70	Transradial catheterization.
Varenne 2014 [31]	RCT	NR	France	1950	NR	NR	Transradial catheterization.
Xiaolong 2012 [32]	RCT	NR	China	180	NR	54	Transradial catheterization.

RCT=randomized controlled trial, NR=not reported

Table 2: Intra-arterial vasodilator treatments, results and interpretation.

Study ID	Treatments	Results	Interpretation
Abe 2000 [12]	Saline, ISDN 1 mg, 3 mg, 5 mg, verapamil 1 mg, 3 mg, 5 mg, lidocaine 10 mg, 30 mg, 50 mg, n=10 in each group.	Change ratio: (diameter after drug injection - diameter before drug injection) x 100/(diameter before drug injection) for proximal and distal: saline 3.1%/6.1%, ISDN 1 mg 19.1%/20.3%, 3 mg 17.4%/18.6%, 5 mg 31.0%/28.8%, verapamil 1 mg 6.4%/14.6%, 3 mg 4.3%/7.6%, 5 mg 9%/10.8%, lignocaine 10 mg -15.6%/-12.1%, 30 mg -12.7%/-17.3%, 50 mg -7.3%/-1.6%.	ISDN was most potent vasodilator compared to verapamil, lignocaine and placebo.
Boyer 2013 [13]	Verapamil 200ug/nitroglycerin 200ug (n=43), placebo (n=78)	Radial artery origin: no vasodilator 2.09±0.41 mm, vasodilator 2.29±0.47 mm, p=0.022. Radial artery narrowest segment: no vasodilator 1.39±0.43 mm, vasodilator 1.83±0.56, p<0.001 mm.	Nitroglycerin and verapamil was associated with greater vasodilation compared to placebo.
Byrne 2008 [14]	Verapamil 1 mg, magnesium sulphate 150 mg.	Increase in radial artery: magnesium 0.36±0.03mm, verapamil 0.27±0.03mm, p<0.05. Decrease in MAP with verapamil -6.6±1.4 mmHg, p<0.01, magnesium -0.25±1.4 mmHg, p=NS. Vagal reaction requiring IV atropine: verapamil 3, magnesium 1.	Magnesium is a more potent vasodilator than verapamil.
Carrilo 2011 [15]	Nitroglycerin 200 ug/verapamil 2.5 mg (n=15), verapamil 2.5 mg (n=15).	Relative diameter increase: nitroglycerin/verapamil 6.6±6.7, verapamil 8.6±14.5, p=0.69.	Similar vasodilation can be achieved with verapamil with and without nitroglycerin.
Chen 2006 [16]	Nitroglycerin 100ug/verapamil 1.25 mg (n=133), nitroglycerin 100ug (n=135), placebo (n=93).	RAS rate: nitroglycerin/verapamil 5/133, nitroglycerin 6/135, placebo 19/93.	Similar rates of RAS with nitroglycerin with and without verapamil which were lower than placebo.
Cho 2008 [17]	Nicorandil 12 mg (n=72), nitroglycerin 200ug/verapamil 100ug (n=72).	Change in radial artery diameter as proximal segment: nicorandil 1.58 to 1.92 mm, nitroglycerin/verapamil 1.67 to 1.93 mm. Change of minimal luminal diameter: nicorandil 0.63 vs nitroglycerin/verpamil 0.48. RAS rate (proximal and middle segment): nicorandil 37/72, nitroglycerin/verapamil 51/72, proximal only nicorandil 22/72, nitroglycerin/verapamil 24/72, middle segment nicorandil 15/72, nitroglycerin/verapamil 27/72.	Nicorandil is not superior to nitroglycerin and verapamil as a vasodilator.
Coppola 2006 [18]	Nitroglycerin 100 ug/diltiazem 5 mg (n=123), nitroprusside 100 ug/diltiazem 5 mg (n=119), nitroglycerin 100 ug/nitroprusside 100ug/diltiazem 5 mg	Radial artery diameter: nitroglycerin/diltiazem 2.37 mm, nitroprusside/diltiazem 2.36 mm, nitroglycerin/nitroprusside/diltiazem 2.33mm. RAS rate: nitroglycerin/diltiazem 15/123, nitroprusside/diltiazem	No improvement in RAS with nitroglycerin/diltiazem, nitroprusside/diltiazem and nitroglycerin/nitroprusside/diltiazem.

	(n=137).	16/119, nitroglycerin/nitroprusside/diltiazem 13/137.	
Dalal 2011 [19]	Nitroglycerin 200 ug/diltiazem 5 mg (n=100), nicorandil 4 mg (n=100).	Decrease in radial artery diameter in proximal segment: nitroglycerin/diltiazem 80±48%, nicorandil 80±37%. Decrease in systolic blood pressure: nitroglycerin/diltiazem 13±9, nicorandil 6±5.	Similar decreases in radial artery diameter with nicorandil compared to nitroglycerin/diltizem but there is less blood pressure drop with nicorandil.
Dharma 2012 [20]	Nitroglycerin 200 ug/diltiazem 2.5 mg (n=75), nitroglycerin 200 ug (n=75).	Procedural success 100% in both groups. Systolic BP nitroglycerin/diltiazem 162.68±27.68 to 125.56±21.30 mmHg, nitroglycerin 161.12±27.54 to 141.24±26.15 mmHg. Diastolic BP nitroglycerin/diltiazem 80.11±11.03 to 71.60±11.21 mmHg, nitroglycerin 78.31±13.61 to 75.88±11.45 mmHg. Heart rate nitroglycerin/diltiazem 81.69±18.37 to 86.61±18.05, nitroglycerine 81.61±17.27 to 84.69±18.08.	Similar rates of procedural success with nitroglycerin with and without diltiazem.
Hizoh 2014 [21]	Verapamil 5 mg (n=294), placebo (n=297).	RAS rate: verapamil 5/294 (1.0%), placebo 3/297 (1.7%).	Lower rates of RAS with verapamil compared to placebo.
Kiemeneij 2003 [22]	Verapamil 5 mg/nitroglycerin 200 ug (n=50), placebo (n=50).	Maximum pullback force: verapamil/nitroglycerine 0.53±0.52, placebo 0.76 ± 0.45. RAS rate: verapamil/nitroglycerin 4/50, placebo 11/50.	RAS lower with verapamil/nitroglycerin compared to placebo.
Kim 2007 [23]	Nicorandil 4 mg (n=75), verapmil 200 ug (n=75).	Blood pressure change: nicorandil reduced by 15.4±11.5 mmHg, verapamil reduced by 16.3±13.4 mmHg. Change in diameter: proximal nicorandil 2.59±0.49 mm to 2.91 ±0.48 mm, verapamil 2.62±0.57 mm to 2.89±0.56 mm. Mid-segment increase nicorandil was 0.34±0.23 mm, verapamil 0.24±0.15 mm. RAS rate: nicorandil 39/75 (50.7%) vs verapamil 39/75 (52%).	Similar RAS rates with nicorandil and verapamil.
Manickam 2011 [24]	Verapamil/nitroglycerin (likely n=300), nicorandil 2 mg (likely n=300).	RAS rate: nicorandil 3% (likely 9/300), verapamil/nitroglycerin 12% (likely 36/300).	RAS lower with nicorandil compared to verapamil/nitroglycerin.
Mont'AlverneFino 2003 [25]	ISMN (n=23), diltiazem/ISMN (n=27).	Radial artery diameter: ISMN before 2.39±0.45 mm after 2.35±0.47 mm, diltiazem/ISMN before 2.15±0.32 mm after 2.46±0.39 mm. Radial artery output ISMN before 7.07±5.37 ml/min after 5.89±3.33 ml/min, diltiazem/ISMN before 5.74±2.79 ml/min after 9.06±7.78 ml/min. RAS rate: ISMN 1/23, diltiazem/ISMN 0/27. Radial spasm, occlusion, partial occlusion: ISMN 4/23, diltiazem/ISMN 0/27.	RAS rates similarly low in ISMN and diltiazem ISMN but study is underpowered.
Rosencher 2012 [26]	Diltiazem 5 mg (n=117), verapamil 2.5 mg (n=109), ISDN 1 mg (n=106).	RAS rate (severe and minor): ISDN 22/106 (21%), verapamil 23/109 (21%), diltiazem 42/117 (26%).	Higher rates of RAS with diltiazem compared to ISDN and verapamil.

Rosencher 2013 SPASM 3 [27]	Diltiazem (n=252), verapamil (n=235), ISDN (n=244).	RAS rate: diltiazem 67/252 (26.6%), verapamil 38/235 (16.2%), ISDN 42/244 (17.2%).	Higher rates of RAS with diltiazem compared to ISDN and verapamil.
Ruiz-Salmeron 2005 [28]	Petolamine 2.5 mg (n=250), verapamil 2.5 mg (n=250).	Change in diameter petolamine 12.6±12.9%, verapamil 13.6±14.5%. RAS rate: verapamil 33/250 (13.2%), pentolamine 58/250 (23.2%). Radial semiocclusion and occlusion: verapamil 19/250 (7.7%), pentolamine 16/250 (6.4%).	Radial semi-occlusion and occlusion with verapamil and pentolamine.
Sakai 1999 [29]	ISDN 1m g, nitroglycerin 1 mg, verapamil 5 mg.	Enlargement greatest with nitroglycerine 12.7% vs ISDN and verapamil.	Greater vasodilation with nitroglycerine compared to ISDN and verapamil.
Varenne 2006 SPASM 1 and 2 [30]	Verapamil 2.5 mg (n=409), verapamil 5 mg (n=203), molsidomine 1 mg (n=203), verapamil 2.5 mg/molsidomine 1 mg (n=206), placebo (n=198).	RAS rate: placebo 44/198 (22.2%), verapamil 2.5 mg 34/409 (8.3%), verapamil 5 mg 16/203 (7.9%), mosidomine 1 mg 27/203 (13.3%), verapamil/mosidomine 10/206 (4.9%). No difference in symptomatic hypotension.	RAS is lowest with verapamil/mosidomine combination.
Varenne 2014 [31]	Diltiazem, verapamil, mosidomine, isosorbidedinitrate or placebo.	RAS rate: placebo 44/198 (22.2%), molsidomine 27/203 (13%), verpamil 88/847 (10.4%), similiar for placebo ISDN and diltiazem. Significant blood pressure fall occurred more with diltiazem and ISDN.	RAS lowest with verapamil and/or molsidomine and ISDN and diltiazem should be not be used.
Xiaolong 2012 [32]	Nitroglycerine 200 ug (n=60), nicardipine 200ug (n=60), nicardipine 200ug/nitroglycerine 100 ug (n=60).	RAS rate: baseline nitroglycerin 9/60 (15%), nicardipine 5/60 (8.3%), combination 5/60 (8.3%), 2 min nitroglycerin 1/60 (1.7%), nicardipine 2/60 (3.3%) and combination 0/60 (0%).	Nitroglycerin and nicardipine are effective at lowering RAS but combination is best.

ISDN=isosorbide dinitrate, MAP=mean arterial pressure, ISMN=isosorbide mononitrate, RAS=radial artery spasm

Table 3: Single intra-arterial agents and rates of radial artery spasm stratified by whether there were single or multiple study results.

Intra-arterial agent	Total studies	Total RAS	Total participants	Rate of RAS
Multiple studies				
Placebo	4	77	638	0.12
Verapamil 2.5 mg	3	90	768	0.12
Verapamil 5 mg	2	21	497	0.04
Nicorandil (variable dose)	3	70	447	0.16
Single studies				
Nitroglycerin 100 µg	1	6	135	0.04
Nitroglycerin 200 µg	1	1	60	0.02
ISMN	1	1	23	0.04
Diltiazem	1	67	252	0.27
Nicardipine	1	2	60	0.03
Pentolamine	1	58	250	0.23
Mosidomine	1	23	203	0.11

RAS=radial artery spasm

Table 4: Other outcomes of studies which evaluated intra-arterial vasodilators.

Study ID	Procedure time	Bleeding reported	Sheath information	Procedure Failure	Radial occlusion
Abe 2000 [12]	NA	NA	NA	NA	NA
Boyer 2013 [13]	NA	NA	Terumo glidesheath	NA	NA
Byrne 2008 [14]	Longer in treatment arm	NA	Hydrophilic sheaths in treatment arm	NA	NA
Carrilo 2011 [15]	NA	NA	Hydrophilic sheaths both arms	NA	NA
Chen 2006 [16]	NA	NA	Hydrophilic sheaths both arms	NA	NA
Cho 2008 [17]	Longer in placebo arm	NA	NA	NA	NA
Coppola 2006 [18]	Recorded but not quoted in paper	NA	Non hydrophilic sheaths all arms	NA	NA
Dalal 2011 [19]	NA	NA	NA	NA	NA
Dharma 2012 [20]	NA	NA	Hydrophilic sheaths	NA	NA
Hizoh 2014 [21]	Not significant both arms	NA	NA	Not significant both arms	NA
Kiemeneij 2003 [22]	Not significant both arms	NA	NA	NA	NA
Kim 2007 [23]	NA	NA	NA	NA	NA
Manickam 2011 [24]	NA	NA	NA	NA	NA
Mont'AlverneFino 2003 [25]	NA	NA	NA	NA	NA
Rosencher 2012 [26]	NA	NA	NA	Not significant	NA
Rosencher 2013 SPASM 3 [27]	NA	NA	NA	NA	NA
Ruiz-Salmeron 2005 [28]	NA	NA	NA	Significant in treatment arm	NA
Sakai 1999 [29]	NA	NA	NA	NA	NA
Varenne 2006 SPASM 1 and 2 [30]	NA	NA	Hydrophilic sheaths	NA	NA
Varenne 2014 [31]	Not significant both arms	Not significant both arms	Hydrophilic sheaths	NA	NA
Xiaolong 2012	NA	NA	NA	NA	NA

[32]					

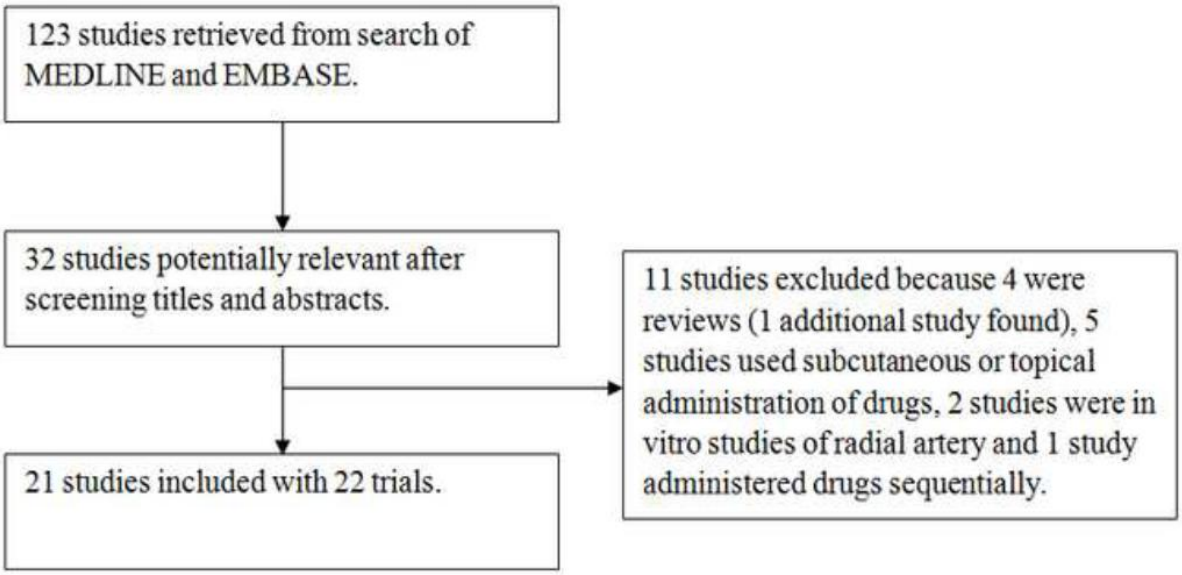
NA=not available

Table 5: Adverse events reported by included studies

Study ID	Adverse events
Abe 2000 [12]	All patients who received ISDN complained of a cold sensation, and all that received verapamil complained of a hot sensation at the injection site of the forearm.
Boyer 2013 [13]	There were no access related complications for either group.
Byrne 2008 [14]	Administration of verapamil resulted in a fall in mean arterial pressure (change in MAP -6.6±1.4 mmHg; p<0.01), whereas magnesium did not have a significant hemodynamic effect (change in MAP -0.25±1.4 mmHg; p=NS). No change in heart rate was seen following administration of either drug (change in HR following study drug; magnesium +0.4±1.5 bpm versus verapamil -0.8±0.9 bpm; p=NS). Three patients in the verapamil group and 1 in the magnesium group suffered vagal reactions requiring treatment with intravenous atropine. Mean pain scores were similar between both groups. Severe arm pain (pain score>5) was observed in 14 (30%) patients receiving verapamil and 9 (27%) receiving magnesium (p=NS).
Carrillo 2011 [15]	No adverse events reported.
Chen 2006 [16]	No adverse events reported.
Cho 2008 [17]	The reductions in the systolic and diastolic blood pressure 1 minute after drug administration were 33.6±11.4/10.4±7.7 mmHg in the Nicorandil group and 12.8±9.8/3.8±5.3 mmHg in the Cocktail group (p<0.001).
Coppola 2006 [18]	No adverse events reported.
Dalal 2011 [19]	No edema was observed in the nitroglycerin and diltiazem group, though 3 patients in the nicorandil group developed edematous swelling locally. Significantly greater increase in heart rate (11±11 vs 5±4, p<0.001) and systolic blood pressure (13±9 vs 6±5, p<0.001) in the nitroglycerin and diltiazem group compared to nicorandil group.
Dharma 2012 [20]	Diltiazem and nitroglycerin vs nitroglycerin significant difference in systolic blood pressure (124.56±21.30 vs 141.24±26.15, p<0.001) and diastolic blood pressure (71.60±11.21 vs 75.88±11.45, p=0.022 but not heart rate (86.61±18.05 vs 84.69±18.08, p=0.516) after cocktail. Vasovagal reaction was higher (3% vs 0%, p=0.497) but not significant in diltiazem and nitroglycerin but there was significantly more local burning pain (21% vs 9%, p=0.041).
Hizoh 2014 [21]	There was no considerable difference in the rates of "significant pain" defined as pain score ≥4 on the 1-to-6 scale (Fisher's exact test, placebo 8.8% versus verapamil 7.1%, p=0.45).
Kiemeneij 2003 [22]	More pain (score ≥III) in no cocktail group compared to nitroglycerin and verapamil (34% vs 14%, p=0.019) and pain score was higher in no cocktail group (2.08±1.07 vs 1.7±0.94, p=0.03).
Kim 2007 [23]	No significant differences in the mean change of systolic blood pressure (p=0.61) and diastolic blood pressure (p=0.27) were observed between the two groups.
Manickam 2011 [24]	No adverse events reported.
Mont'AlverneFino 2003 [25]	Only 1 patient (2%) from placebo group had hypotension after injection of the solution. A small hematoma was observed at the site of puncture in 2 cases (4%) but unclear in which group.
Rosencher 2012 [26]	There was also no significant difference in term of safety events and pain sensation between the different groups.
Rosencher 2013 SPASM 3 [27]	No significant difference was found between the three groups in terms of severe pain, crossover and safety events.
Ruiz-Salmeron 2005 [28]	There were only two serious events related to the procedure: one patient presented an extensive hematoma in the right forearm produced by radial

	perforation and was managed conservatively; another patient developed a transient cerebrovascular accident, with no permanent sequel. Mean aortic pressure drop after vasodilator was greater in the phentolamine group compared to verapamil (14.2±8.0 vs 8.8±6.8, p<0.001).
Sakai 1999 [29]	No adverse events reported.
Varenne 2006 SPASM 1 and SPASM 2 [30]	Symptomatic hypotension occurred in 73 patients (6%) with no difference between groups. Morphine chlorydrate was administered because of per-procedural arm pain in 36 patients (3%) with no difference between groups. Minor hematomas were noted in 70 patients (5.7%), and the absence of a left radial pulse with no ischemia occurred in 12 (1%).
Varenne 2014 [31]	Significant fall of blood pressure occurred significantly more with diltiazem and ISDN compared to placebo or other vasodilators (p=0.001).
Xiaolong 2012 [32]	No adverse events reported.

Figure 1: Flow diagram of study selection



Highlights

- Radial artery spasm(RAS) causes procedural failure in transradial catheterization.
- RAS may complicate 10-15% procedures undertaken through the radial approach.
- We reviewed the efficacy of vasodilators that have been used to minimize RAS.
- The pooled RAS rate was lowest with 5 mg of verapamil(4%) compared to placebo(12%).
- The best combination of drugs to minimize RAS is nitroglycerine and verapamil.