BET 3: PERIPHERAL METARAMINOL INFUSION IN THE EMERGENCY DEPARTMENT

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ABSTRACT

A short cut review was carried out to establish whether peripheral metaraminol infusions can be safely and effectively used in emergency department patients. 239 papers were found of which 8 presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. The clinical bottom line is that despite anecdotal evidence of common usage there is limited high quality evidence to support the use of peripheral metaraminol as vasopressor support in the emergency department.

THREE-PART QUESTION

In (adult patients presenting to the ED with sepsis resulting in persistent hypotension not responding to fluid replacement) is a (peripheral metaraminol infusion as effective as central catecholamine infusion) for (maintaining a blood pressure capable of effective organ perfusion)?

CLINICAL SCENARIO

A previously fit and well 36-year-old male returns from a holiday to Greece 48 hours ago and presents to the ED complaining of headache, malaise and feeling generally unwell. While waiting to be seen, the patient's headache rapidly worsens, he spikes a high temperature of 38.9°C, becomes increasingly agitated and starts vomiting. He is taken to a resuscitation cubicle and has a HR of 135 bpm and BP of 71/45 mm Hg. Examination of the patient reveals several small non-blanching petechiae. You manage the patient as suspected meningitis and commence appropriate sepsis management. After administrating 3 L of intravenous fluid, the patient remains with a systolic BP <80 mm Hg. The intensive care doctor informs you that they are trying to make a space available in the intensive treatment unit for this patient but are struggling to step anyone down and the patient must remain in the resuscitation department. The resuscitation nurse asks you to prescribe more fluid. You wonder whether a peripheral metaraminol infusion would be more effective at increasing arterial pressure and maintaining organ perfusion.

SEARCH STRATEGY

Ovid MEDLINE (1946 to present).
EMBASE (1974 to present)
CINAHL (1981 to present)
ProQuest Database
Pubmed Database
Cochrane Database
NICE Evidence Database
College of Emergency Medicine

A grey literature search was performed via www.google.com, www.opengrey.eu and www.controlled-trials.com

([metaraminol.mp or exp metaraminol] OR [aramine.mp or exp aramine] OR [levicor.mp] AND [noradrenaline.mp or exp norepinephrine] OR [adrenaline.mp or exp epinephrine] AND [sepsis.mp or sepsis] OR [hypotension.mp or hypotension]).

The references and citations of review articles were also searched for articles relevant to the three-part question.

SEARCH OUTCOMES

MEDLINE search produced 35 papers. EMBASE search produced 5 papers. CINAHL search produced 4 papers. ProQuest search produced 55 papers. PubMed search produced 150 papers. Cochrane database revealed one article of interest, but I was unable to obtain bar a worldwide search and translation. NICE Evidence search identified no additional relevant articles.

College of Emergency Medicine website contained no relevant evidence or guidelines. The Australian, American, Canadian and New Zealand colleges of emergency medicine were searched but contained no relevant evidence or guidelines.

Citations from articles of interest were also searched and revealed several new articles which appeared relevant to the three-part question. However, these were all predated publications from 1964. For most articles, I was unable to obtain an abstract, the abstract was in a foreign language and I was unable to obtain any articles in full via internet or library searches.

In total, eight articles were identified that were relevant to the three-part question (table 3).

COMMENTS

Natalini *et al* specifically focused on the comparison of noradrenaline and metaraminol as a vasopressor for the management of septic shock and revealed that there was no significant difference in patient's cardiac output, haemodynamic variables or acid–base status. They also found that there was no relationship in the doses provided to achieve patient optimisation. Hou *et al* demonstrated that metaraminol infusion caused no statistical difference to renal function over time regardless of the infusion strength. Makowski *et al* conducted a small study which demonstrated that metaraminol can be given to good effect peripherally and potentially be used for long periods of time. The remaining studies demonstrated that metaraminol was an effective treatment for managing shock when compared with other vasopressor therapies, both in terms of drug efficacy and patient mortality. All of the studies were small retrospective or prospective cohort studies, with one small crossover trial, at which the level of evidence was not very strong. One of the studies was identified as a poster presentation at an International anaesthetic conference had only ever been published in abstract form, making appraisal of the study findings impossible. All the papers had low numbers of patients, there were no

Table 3 Relevant papers

Author, year, country of publication	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Natalini *et al* 2005,[1] Italy	10 patients admitted to a single Italian medical and surgical intensive care unit who met following inclusion criteria: (1) diagnosis of septic shock, (2) adequate fluid resuscitation and pulmonary artery occlusion pressure >14 mm Hg, (3) use of norepinephrine to maintain MAP >65 mm Hg. Norepinephrine and metaraminol	Prospective cohort study (level 2b)	1. Detection of cardiac output >30%	1. No significant difference demonstrated in stroke volume index (mL/beats/m²) norepinephrine (40±15) metaraminol (40±15) (p=0.991) and HR (beats/min) norepinephrine (96±15) metaraminol (95±21) (p=0.863)	No randomisation of study drugs. No blinding of physicians or patients (although does state that this was considered unethical for the patient group being studied). Small patient numbers
			2. Haemodynamic variables	2. No significant difference demonstrated in global haemodynamic variables	
			3. Drug doses	3. No relationship between norepinephrine (0.30±0.28 µg/kg/min) and metaraminol (2.5±1.7 µg/kg/min) doses (R^2=0.087)	
			4. Patient acid–base status	4. No difference in acid–base status between norepinephrine (– 4.2/–3.9) and M (–4.2/–3.8) (p=0.919)	
Hou *et al*, 2007,[2] China	Single centre study. 98 patients with septic shock (using Hurford's diagnostic criteria) were divided into three groups (A, B, C) according to highest infusion rate of metaraminol used (0.1–0.5, 0.6–1.0, >1.0 µg/kg), respectively	Retrospective cohort. Observational study (level 2b)	1. Apache III 2. Urine output (mL/hour) 3. U-ALB (mg/L) 4. Uβ2-MG (mg/L) 5. BUN (mmol/L) 6. CRE (µmol/L)	No statistical significant differences in the changes of these renal function parameters with time among the three groups	No power calculation. No control group. Unclear inclusion/exclusion criteria. Retrospective reporting bias
Makowski and Misztal, 2010,[3] UK	47 patients (25 female, 22 male) admitted to single-centred surgical HDU who were started on peripheral metaraminol infusion	Prospective observational study (level 3)	1. Reason for starting metaraminol	1. Sepsis 34%, others 66%	Abstract only. Poster presentation at the Lisbon International Anaesthesia Conference 2012. Small patient numbers
			2. Average infusion time	2. 37.62 hours (range 1.5–144 hours)	
			3. Central line insertion (%)	3. CVCs inserted in 36% of patients	
			4. Fluid balance (before/after metaraminol infusion) (mean±SD)	4. 12 hours before infusion 2570.64±1198.01 mls 12 hours after infusion 985±377.61 mls (p=0.0001)	
Udhoji *et al*, 1964,[4] USA	12 patients with hypotension and clinical features of shock from varying aetiology. Levarterenol (noradrenaline, norepinephrine) Metaraminol or angiotensin were administered by intravenous infusion Six patients received angiotensin first followed by levarterenol or metaraminol. The other six patients received levarterenol or metaraminol followed by angiotensin	Prospective crossover study (level 2b)	1. Cardiac index	1. Cardiac indexes were lower in all cases during infusion of angiotensin vs levarterenol (1.7 vs 2.0 L/min/sq m) (p<0.01) or metaraminol (1.8 vs 2.8 L/min/sq m) (p, 0.01)	Old publication—less generalisable. Small patient numbers (no power calculation). No blinding. No description of randomisation technique. Urine flow data difficult to interpret. No washout period between different drugs. No attempt to exclude confounding factors
			2. Urine flow	2. In 10 of 12 patients urine flow was significantly reduced during angiotensin infusion compared with metaraminol or levarterenol.	
Mills *et al*, 1960,[5] USA	67 patients with shock from varying aetiology were given one or combination of mephentermine, metaraminol, phenylephrine, levarterenol, epinephrine and methoxamine. Patients were selected at random and treated by resident staff and faculty	Prospective cohort observation study (level 3)	1. Shock due to MI	1. 20 patients. 13 survived. Survival rate in those with metaraminol exceeded previously reported with use of levarterenol	Old publication—less generalisable. No description of inclusion criteria. Unclear methodology as how drugs were given, for how long, in which combination. Results section confusing as it lists results from various other studies (both animal and human trials). No attempt at randomisation, blinding or exclusion of confounding factors
			2. Shock due to sepsis	2. Nine patients. One survived, three had satisfactory response to vasopressor therapy and were normotensive at death	
			3. Shock due to haemorrhage	3. Seven patients. Two survived. All those who failed to respond to metaraminol also failed to respond to levarterenol	
			4. Shock due to various causes	4. 31 patients. 11 survived. All those who failed to respond to metaraminol were given levarterenol. Only one of those could reverse shock with eventual survival	

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Table 3 Continued

Author, year, country of publication	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Moyer and Beazley, 1955,[6] USA	20 patients in clinical shock of various aetiology. Ages ranged from 23 to 93 years old (average age 63 years). 14 males and 6 females. Given metaraminol infusion alone or in combination with noradrenaline	Prospective cohort observational study (level 3)	1. Efficacy of metaraminol infusion 2. Administration doses	1. 19/20 patients had a satisfactory response within 8–10 min of infusion commencement. Duration of therapy lasted from 5 to 231.5 hours 2. Metaraminol was approximately 1/20 to 1/25 as potent as norepinephrine during intravenous administration	Old publication—less generalisable. No attempt at randomisation, blinding or exclusion of confounding factors. Small patient numbers
Weil , 1955,[7] USA	42 patients included from four hospitals. All diagnosed with unequivocal shock of various aetiology. Age range 12–84 years (median age 61 years). 18 were given metaraminol infusion alone, 24 were treated with other vasopressor agents and effects were compared	Prospective multicentred cohort observational study (level 2b)	1. Initial response to therapy 2. Satisfactory maintenance to therapy 3. Mortality 4. Comparison with other agents	1. 36 (86%) established prompt systolic BP of ≥100 mm Hg 2. 32 (76%) established sustained systolic BP of ≥100 mm Hg 3. 16 (38%) survived to discharge 4. Norepinephrine gave a pressor response in five not responding to metaraminolFour of these subsequently died. Methoxamine achieved a less satisfactory response than metaraminol when given both intramuscular and intravenous in five patients. Phenylephrine also produced a weaker effect when compared in two patients.	Old publication—less generalisable. Small patient numbers. No attempt at randomisation, blinding or exclusion of confounding factors
Stechel *et al*, 1956,[8] USA	250 patients admitted to a single centre in which the use of a vasopressor was indicated for shock of varied aetiology received metaraminol infusion. 42 cases reported in detail (remaining 208 cases were not included due to insufficient data concerning diagnosis or response to the drug)	Retrospective observational study (level 3)	1. Mortality 2. Efficacy of metaraminol infusion	1. 15 (36%) survived to hospital discharge. 27 (64%) died during this admission 2. No response to BP in six (14%) patients. Noradrenaline substituted in 12 patients who had no prompt response to metaraminol, all of whom died despite this.	Old publication—less generalisable. Small patient numbers. No attempt at randomisation, blinding or exclusion of confounding factors

MAP, mean arterial pressure.

randomised trials and the outcomes were not always clear. Several of the publications were written in an unorthodox format which is likely a reflection of the period from which they were published, making appraisal of the data very difficult and applicability to modern medicine practice questionable. None of the papers used blinding or randomisation techniques, and only Natalini *et al* set out a detailed inclusion criteria to attempt to reduce confounding factors. Several of the selected papers were published over 50 years ago, making them no longer generalisable among modern medicine practice, while the Chinese patient group from Hou *et al* may not be reflective of a typical UK patient demographic.

Anecdotally, we know that peripheral metaraminol is used in UK practice and has many advocates, but this should arguably be tested in a randomised controlled trial with adult patients to compare peripheral metaraminol against alternative circulatory support strategies.

Clinical bottom line

There is limited evidence to support the use of peripheral metaraminol as vasopressor support in ED.

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