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TITLE: Vasopressin as First-Line Therapy for Cardiac Arrest: A Review of the Guidelines and Clinical-Effectiveness

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CONTEXT AND POLICY ISSUES:

Cardiac arrest occurs when mechanical activity of the heart ceases, confirmed by the absence of a detectable pulse, patient unresponsiveness, and apnea, and leads to death if untreated.[1-3] An estimated 70% of cardiac arrests occur outside a hospital,[1] and 75% of cardiac arrests are caused by electrical or mechanical cardiac dysfunction, primarily due to coronary artery disease.[1] The reported incidence of cardiac arrest may vary due to differences in definition and ascertainment.[2] A Canadian study of five geographic regions estimated the annual incidence of out-of-hospital cardiac arrest to range from 53 to 59 per 100,000 population.[1] Based on this estimate and the relative proportion of cardiac arrests occurring out-of-hospital, there are approximately 27,000 cases of cardiac arrest in Canada each year.

Four types of arrhythmias that may produce pulseless cardiac arrest are ventricular fibrillation (VF), rapid ventricular tachycardia (VT), pulseless electrical activity (PEA), and asystole.[4] Survival of these arrest rhythms is dependent on the provision of basic and advanced cardiovascular life support (ACLS).[4] Vasopressors are pharmacologic interventions that are delivered to cardiac arrest patients intravenously during ACLS, with the objective of enhancing aortic diastolic and coronary perfusion pressure as well as coronary and cerebral blood flow and oxygen delivery.[5] Epinephrine (adrenaline) has been the preferred vasopressor used for resuscitating cardiac arrest patients for several decades, however, vasopressin, an antidiuretic hormone, has been evaluated and recommended as an alternative in recent years.[6,7] While there has been some study of the relative effectiveness of these vasopressors (or their combination) in the treatment of the four types of arrhythmias, this issue was identified as a knowledge gap and clinical research priority during the 2005 International Consensus Conference on Emergency Cardiovascular Care and Cardiopulmonary Resuscitation.[8]

The dosages of epinephrine and vasopressin that are commonly used in clinical studies are 1 mg/ml and 40 IU, respectively. The cost of a 40 IU dose of vasopressin in Canada is reported to be C$16.12[9] however it is unclear if there has been a change in this cost in recent years as there has been a change in the United States.[10] The cost of a 1 mg/ml dose of epinephrine ranges from C$0.53 to C$2.61 on some Canadian provincial and territorial formularies.[11-13]

A review of the most recent clinical evidence regarding these drugs would be useful for informing decisions regarding their use. The objective of this report is to review current guidelines as well as the most recent clinical evidence for the use of vasopressin versus epinephrine as first line therapy in the treatment of patients with cardiac arrest.

RESEARCH QUESTION:

What is the clinical-effectiveness of vasopressin as a first-line therapy versus epinephrine for the treatment of adults in cardiac arrest?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID MedLine, OVID Embase, The Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and April 2009. No filters were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS:

The literature search yielded 209 citations, as well as 21 references from the grey literature. The initial screening process resulted in the retrieval of 34 reports for further evaluation. The final screening yielded 13 relevant reports, including seven guidelines, three systematic reviews (one of which also performed a meta-analysis), two randomized control trials (RCTs), and one observational study. No health technology assessments were identified. The reasons for excluding reports were: indication was not cardiac arrest; vasopressin not assessed as a first-line agent; treatment with vasopressin included other agents (ex. corticosteroids or hydroxyethyl starch) that were not provided similarly to the epinephrine group; not a systematic review; and duplicate report.

Guidelines

The Australian Resuscitation Council (ARC) published guidelines for advanced life support in 2006.[14] The guidelines were developed using an evidence-based approach which included a systematic review of the literature. Each recommendation was assigned one of seven levels of evidence (I [highest level of evidence], II, III-1, III-2, III-3, IV, and expert consensus opinion) and one of two levels of recommendation (Class A: Recommended, Class B: Acceptable). Their protocol for advanced life support states that 1 mg/ml adrenaline should be administered every three minutes during CPR once intravenous access is obtained. This treatment is recommended for all rhythms, and is to be carried out continuously or during each loop of the treatment algorithm for adult cardiorespiratory arrest. The guidelines states that other drugs should be considered depending on the individual circumstances. This guideline was a Class A recommendation and the level of evidence was expert consensus opinion. It was noted that there are no placebo-controlled studies that show that the routine use of any vasopressor at any

stage during human cardiac arrest increase survival to hospital discharge, and that current evidence is insufficient to support or refute the routine use of any drug or sequence of drugs, however it is reasonable to continue use of vasopressors on a routine basis in spite of lack of human data (Class B, Level of Evidence II: at least one properly designed RCT). Vasopressin was listed among the drugs used in resuscitation, and the authors stated that while vasopressin is an alternative vasopressor to adrenaline, there is insufficient evidence to support or refute the use of vasopressin as an alternative to, or in combination with, adrenaline in any cardiac arrest rhythm.

In 2006, the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) published guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[3] Guidelines were based on the evidence evaluation from the 2005 International Consensus Conference on Emergency Cardiovascular Care and Cardiopulmonary Resuscitation in collaboration with the International Liaison Committee on Resuscitation (ILCOR), and the recommended algorithm for advanced cardiac life support was obtained from the 2005 AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.[4] During ACLS, epinephrine 1 mg/ml intravenous (IV) is to be administered and followed by repeated defibrillation attempts at 360J, and administration may be repeated at 3- to 5-minute intervals with defibrillator shocks in-between doses. Only one dose of 40 IU IV vasopressin may replace either the first or second dose of epinephrine. This treatment is recommended for all rhythms. The authors note that high-dose epinephrine does not appear to provide added benefit, and evidence for superiority of vasopressin is not clearly established. A level of evidence and grade of recommendation for the use of epinephrine and vasopressin was not specified.

The AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care that were published in 2005[4] were also based on the evidence evaluation from the 2005 International Consensus Conference on Emergency Cardiovascular Care and Cardiopulmonary Resuscitation in collaboration with the ILCOR. Recommendations for use of vasopressors were the same as those in the ACC/AHA/ESC guidelines.[3]

The 2005 International Consensus Conference on Emergency Cardiovascular Care and Cardiopulmonary Resuscitation published their evidence review and recommendations for advanced life support (ALS) in 2005.[15] It is unclear whether the literature review on which the recommendations were based was systematic, however, evidence was appraised for quality and graded with a level of evidence ranging from 1 (RCTs or meta-analyses of multiple clinical trials with substantial treatment effects) to 8 (rational conjecture; common practices accepted before evidence-based guidelines). As with the ARC guidelines,[14] these guidelines stated that no placebo-controlled study had shown that the routine use of any vasopressor at any stage during human cardiac arrest increases survival to hospital discharge. The guidelines also stated that current evidence does not support the use of any drug or sequence of drugs, but continued routine use of vasopressors was reasonable. The treatment recommendation was that epinephrine is the standard vasopressor in cardiac arrest, despite the absence of placebo controlled trials, and there is insufficient evidence to support or refute the use of vasopressin as an alternative to, or in combination with, epinephrine in any cardiac arrest rhythm. The evidence review relating to this recommendation included level 1 studies. Specific recommendations regarding dose and frequency of use of either vasopressor were not provided, however the dosages for vasopressin and epinephrine that were mentioned in the evidence review were 40 IU and 1 mg, respectively.

Both the European Resuscitation Council 2005 Guidelines for Resuscitation[16] and the UK Resuscitation Council Guidelines for Advanced Life Support[17] were in agreement with the 2005 International Consensus Conference on Emergency Cardiovascular Care and Cardiopulmonary Resuscitation[15] and the ARC[14] with regards to evidence, and recommended epinephrine as the first vasopressor used in cardiac arrest of any etiology. One mg/ml adrenaline is to be used intravenously for every 3-5 minutes of CPR.

The ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (2004)[18] were developed using systematic literature search, and recommendations had three classification levels (I [highest], II, and III) and three levels of evidence (A [highest], B, and C). The guidelines recommended that clinicians follow the 2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care published by the AHA and ILCOR with regards to resuscitation methodology. As in 2005,[4] these guidelines recommended that vasopressin 40 IU IV may be substituted for epinephrine 1 mg/ml. In addition, both vasopressin and epinephrine were included among prompt resuscitative measures recommended for the treatment of ventricular asystole (Class I Recommendation; Level of Evidence B: single randomized trial or non-randomized studies).

Systematic reviews and meta-analyses

In 2008, Sillberg et al. published a systematic review that examined the evidence for the combination of vasopressin and epinephrine versus epinephrine alone for cardiac arrest.[19] The literature search included RCTs and clinical trials published up to 2007 which met the following criteria: (1) the study reported outcomes for return of spontaneous circulation (ROSC), survival to hospital admission, or survival to hospital discharge; (2) the study included some patients who received both vasopressin and epinephrine; and (3) the study examined patients with non-traumatic cardiac arrest requiring administration of vasopressors. Three RCTs met these conditions (Stiell [2001], Wenzel [2004], and Callaway [2006]). The study by Wenzel et al.[20] will be described in further detail in this report. The three studies were considered by Sillberg et al. to be too heterogenous to conduct a meta-analysis. A summary description of these trials and their results are provided in Table 1.

Table 1: Summary of Studies in the Systematic Review by Sillberg et al.[19]

Author (Year)	Sample Size	Setting	Intervention	Results	Jadad Score and Allocation Concealment
Stiell et al. (2001)	169	IHCA	40 IU vasopressin vs. 1 mg epinephrine, with non-responders receiving epinephrine	No significant improvement in outcome in patients given vasopressin initially. For patients who survived to hospital discharge, 80% scored highest cerebral performance regardless of treatment.	5, A
Wenzel et al. (2004)	732	OOHCA	40 IU vasopressin, followed by 40 IU vasopressin if needed vs. 1 mg epinephrine followed by 1 mg epinephrine if needed	Significantly improved outcomes in patients initially receiving vasopressin. Outcomes for patients who survived to hospital discharge were poor (slightly worse in the vasopressin group), with many suffering severe cognitive impairment.	3, B
Callaway et al. (2006)	325	OOHCA	1 mg epinephrine + 40 IU vasopressin vs. 1 mg epinephrine + placebo	No significant improvement in outcome in patients given vasopressin.	5, A

IHCA: in-hospital cardiac arrest; OOHCA: out-of-hospital cardiac arrest; Jadad Score assesses study quality on a scale of 0 (low quality) to 5 (high quality); Allocation concealment of randomization assessed as A (adequate), B (inadequate), or C(unable to assess).

Only the studies by Stiell et al. (2001) and Wenzel et al. (2004) address the question of using vasopressin first-line, as all patients in Callaway et al. received epinephrine first-line. Detailed results of the three trials were not provided in this review. The authors noted that in all three studies, patients who responded to the initial drug would not be included in the final analysis and as such, patients included in the study may have been more likely to have a poor outcome, regardless of the drug used. Sillberg et al. concluded that the combination of vasopressin and epinephrine showed trends towards better ROSC but uncertain effects on survival, and that there is inadequate evidence to advocate the sequential use of vasopressin and epinephrine for cardiac arrest.

Koshman et al. (2005)[9] published a systematic review of RCTs of vasopressin for cardiac arrest in humans, and included studies published to June of 2005. Three RCTs were identified (Lindner et al.[1997], Stiell et al.[2001], and Wenzel et al.[2004]), two of which were identified in the systematic review by Sillberg et al.[19] All three trials compared vasopressin with epinephrine. Efficacy outcomes included ROSC, successful resuscitation, survival to hospital admission, 24-hour survival, and survival to hospital discharge. Safety outcomes were defined by each trial. A summary of the three trials is given in Table 2.

Table 2: Summary of Studies in the Systematic Review by Koshman et al.[9]

Author (Year)	Sample Size	Setting/ Rhythm	Intervention	Results
Lindner et al. (1997)	40	OOHCA/ VF	40 IU vasopressin vs. 1 mg epinephrine	Survival to hospital admission: E:35%;V:70% ROSC: E:55%; V:80% Survival at 24h: E:20%; V:60%* Discharge from hospital: E:15%; 40% GCS (mean) at discharge: E:10.7; V:11.7
Stiell et al. (2001)	200	IHCA/ VF, PEA, asystole	40 IU vasopressin vs. 1 mg epinephrine, with non-responders receiving epinephrine	Successful resuscitation: E:35%; V:39% ROSC: E:59%; V:60% Survival at 24h: E:24%; V:26% Survival to discharge: E:14%; V:12% Survival at 30 days: E:14%; V:13% MMSE (median) at discharge: E:35; V:36 Tachyarrhythmia: E:8%; V:10%
Wenzel et al. (2004)	1219	OOHCA/ VF, PEA, asystole	40 IU vasopressin, followed by 40 IU vasopressin if needed vs. 1 mg epinephrine followed by 1 mg epinephrine if needed	Survival to hospital admission: E:31.2%;V:36.3% ROSC: E:28%; V:24.6% Survival to discharge: E:9.9%; V:9.9% Neurological function at discharge (E/V): Good cerebral performance: (34.8%/32.6%) Moderate cerebral disability: (26.1%/15.2%) Severe cerebral disability: (15.2%/19.6%) Coma/vegetative state: (23.9%/32.6%) Asystole patients only (E/V): Survival to hospital admission: (20.3%/V:29.0%, p=0.02) survival to hospital discharge: (1.5%/4.7%, p=0.04)

IHCA: in-hospital cardiac arrest; OOHCA: out-of-hospital cardiac arrest; VF: ventricular fibrillation; PEA: pulseless electrical activity; E: epinephrine; V: vasopressin; ROSC: return of spontaneous circulation; *p=0.02; GCS: Glasgow coma scale; MMSE: Mini-Mental State Examination

The trial by Lindner et al. reported better outcomes in patients administered vasopressin, with survival at 24 hours being statistically significantly higher compared with patients administered epinephrine. No adverse events were observed in this study. The study by Stiell et al. showed no difference in outcomes in patients randomized to receive vasopressin or epinephrine. Subgroup analyses (by cardiac rhythm) showed significantly better survival to hospital admission (29.0% vs. 20.3%, p=0.02) and survival to hospital discharge (4.7% vs. 1.5%, p=0.04) in patients administered vasopressin among asystole patients compared with patients administered epinephrine. In their discussion of the three trials, Koshman et al. noted that most patients received epinephrine, even if randomized to the vasopressin group. In addition, they questioned the value of the chosen study endpoints and suggested that survival to hospital discharge with intact neurological function is the ultimate endpoint, however studies powered to detect such an endpoint would likely require thousands of patients. Finally, the authors noted that sample sizes in two of the three studies were small. They concluded that the evidence for the use of vasopressin in cardiac arrest is indeterminate, that either drug could be considered the first line agent in cardiac arrest, and that further research was needed.

Aung and Htay published a systematic review and meta-analysis of vasopressin in cardiac arrest in 2005.[21] Randomized control trials published to February of 2004 that studied humans using relevant target outcomes (eg. morbidity and mortality), were included. Outcome measures evaluated in the meta-analysis included (1) failure of ROSC, (2) death before hospital admission, (3) death within 24 hours, (4) death before hospital discharge, (5) the combination of number of deaths and cognitively impaired survivors. A random-effect model was used because of heterogeneity between studies. Five RCTs of vasopressin versus epinephrine were identified and included in the analyses (Lindner et al. [1997], Li et al. [1999], Lee et al. [2000], Stiell et al. [2001], and Wenzel et al. [2004]), three of which were identified in the systematic reviews by Sillberg et al.[19] and Koshman et al.[9] Patients were from both in-hospital and out-of-hospital settings. Three of the trials (Lindner, Stiell, Wenzel) compared 40 IU IV vasopressin to 1 mg/ml IV epinephrine, while one trial (Li) studied IV vasopressin 0.5 U/kg (low dose) or 1.0 U/kg (high dose), and in a fifth trial (Lee), the doses of vasopressin and epinephrine were 40 IU and 1 mg, respectively, however, the route of administration of the drugs was unclear. Allocation concealment was deemed adequate in three trials (Lindner, Stiell, Wenzel) and unclear in two (Li, Lee). The Jadad score was 5 in three trials (Lindner, Stiell, Wenzel) and 2 in two trials (Li, Lee). A summary of the results of the meta-analyses performed by Aung and Htay is provided in Table 3.

Table 3: Meta-Analyses for Vasopressin Versus Epinephrine by Aung and Htay[21]

Outcome	Trials included	Vasopressin Events/total patients	Epinephrine Events/total patients	RR (95%CI)	Test for heterogeneity	Overall effect
ROSC failure	Lindner (1997) Li (1999) Lee (2000) Stiell (2001) Wenzel (2004)	507/758	511/761	0.81 (0.58-1.12)	$X^2_{(T-1)}$=12.08 (p=0.02) I^2=66.9%	Z=1.29 (p=0.20)
Death before hospital admission	Lindner (1997) Wenzel (2004)	381/609	424/617	0.72 (0.38-1.39)	$X^2_{(T-1)}$=3.36 (p=0.07) I^2=70.2%	Z=0.97 (p=0.33)
Death within 24 hours	Lindner (1997) Stiell (2001)	85/124	89/116	0.74 (0.38-1.43)	$X^2_{(T-1)}$=4.99 (p=0.03) I^2=80.0%	Z=0.90 (p=0.37)
Death before hospital discharge	Lindner (1997) Li (1999) Lee (2000) Stiell (2001) Wenzel (2004)	657/747	673/752	0.96 (0.87-1.05)	$X^2_{(T-1)}$=8.05 (p=0.09) I^2=50.3%	Z=0.92 (p=0.36)
Deaths + cognitively impaired survivors	Lindner (1997) Li (1999) Lee (2000) Stiell (2001) Wenzel (2004)	648/676	650/677	1.00 (0.94-1.07)	$X^2_{(T-1)}$=3.03 (p=0.22) I^2=33.9%	Z=0.11 (p=0.91)

ROSC: return of spontaneous circulation; RR: risk ratio of outcome while on vasopressin (pooled estimate).

The authors also conducted three subgroup meta-analyses based on cardiac rhythm (VF or VT, PEA, and asystole) on the outcome of death before hospital discharge, and found no important differences between vasopressin and epinephrine groups in any of the three analyses (risk ratios ranged from 0.97 to 1.02). The authors concluded that their findings demonstrated no clear benefit or evidence of harm for the use of vasopressin versus epinephrine in cardiac arrest, and that guidelines for ACLS should not recommend vasopressin in resuscitation protocols until more solid human data on superiority are available.

Randomized controlled trials

In 2004, Wenzel et al.[20] published the results of a RCT of vasopressin and epinephrine in out-of-hospital CPR. The results of this study have been previously referred to in the three systematic reviews discussed in this report.[9,19,21] The study was conducted in Germany, Austria, and Switzerland from June 1999 to March 2002. Adult patients with out-of-hospital cardiac arrest and presenting with VF, PEA, or asystole requiring CPR with vasopressor therapy were included. Exclusion criteria were: patients less than 18 years of age, successful defibrillation without a vasopressor, pregnancy, traumatic cardiac arrest, a documented terminal illness, lack of intravenous access, hemorrhagic shock, or presence of a do-not-resuscitate order. The primary and secondary endpoints were survival to hospital admission, and survival to hospital discharge, respectively, however, ROSC and cerebral performance among all patients who survived to discharge were also examined. Endpoints were analyzed for all patients and by cardiac rhythm type as well. Randomized patients received either up to two ampoules of 1 mg epinephrine to be administered every three minutes during CPR, or up to two ampoules of 40 IU vasopressin to be administered every three minutes during CPR. If spontaneous circulation was not restored after the two ampoules of study medication, patients were thereafter given additional injections of epinephrine at the discretion of an emergency physician. All drugs were injected intravenously. A total of 589 patients randomized to receive vasopressin and 597 patients randomized to receive epinephrine, were included in the analysis. Patients were comparable with regards to baseline characteristics, including age, sex, cardiovascular history, whether the arrest was witnessed, CPR administration by a bystander, suspected cause of cardiac arrest, treatments given during CPR, cardiac rhythm, duration of untreated cardiac arrest, and time to basic life support. The average age of patients was 66 years and 70% were male. Outcomes for all 1186 patients showed no between-group differences for any of the outcomes, however patients with asystole cardiac rhythms had significantly better survival to hospital admission and survival to hospital discharge when randomized to vasopressin (see Table 4 below).

Table 4: Outcomes for all 1186 Patients in Wenzel et al.[20]

Variable	Vasopressin (n=589)	Epinephrine (n=597)	p-value	Odds Ratio (95%CI)
All patients				
ROSC with study drugs	145/589 (24.6%)	167/597 (28.0%)	0.19	1.2 (0.9-1.5)
Hospital admission	214/589 (36.3%)	186/597 (31.2%)	0.06	0.8 (0.6-1.0)
Hospital discharge	57/578 (9.9%)	58/588 (9.9%)	0.99	1.0 (0.7-1.5)
Asystole				
ROSC with study drugs	42/262 (16.0%)	44/266 (16.5%)	0.87	1.0 (0.7-1.6)
Hospital admission	76/262 (29.0%)	54/266 (20.3%)	0.02	0.6 (0.4-0.9)
Hospital discharge	12/257 (4.7%)	4/262 (1.5%)	0.04	0.3 (1.0-1.0)

CI: confidence interval; ROSC: return of spontaneous circulation

A post-hoc analysis of 732 patients who had initially received the study medication they were randomized to (ie. two ampoules vasopressin or two ampoules epinephrine), and subsequently received additional treatment with epinephrine at the discretion of the emergency physician administering CPR, showed significantly better outcomes for all patients on vasopressin, as well as with ROSC in patients with VF, and all outcomes in patients with an asystole rhythm (Table 5).

Table 5: Outcomes for 732 Patients who had Initially Received Study Medication and Subsequently Received Additional Treatment with Epinephrine in Wenzel et al.[20]

Variable	Vasopressin (n=373)	Epinephrine (n=359)	p-value	Odds Ratio (95%CI)
All patients				
ROSC with study drugs	137/373 (36.7%)	93/359 (25.9%)	0.002	0.6 (0.4-0.8)
Hospital admission	96/373 (25.7%)	59/359 (16.4%)	0.002	0.6 (0.4-0.8)
Hospital discharge	23/369 (6.2%)	6/355 (1.7%)	0.002	0.3 (0.1-0.6)
Ventricular fibrilation				
ROSC with study drugs	58/122 (47.5%)	40/122 (32.8%)	0.02	0.5 (0.3-0.9)
Hospital admission	37/122 (30.3%)	25/122 (20.5%)	0.08	0.6 (0.3-1.1)
Hospital discharge	13/121 (10.7%)	6/121 (5.0%)	0.09	0.3 (0.2-1.2)
Asystole				
ROSC with study drugs	61/187 (32.6%)	39/181 (21.5%)	0.02	0.0 (0.4-0.9)
Hospital admission	42/187 (22.5%)	24/181 (13.3%)	0.02	0.5 (0.3-0.9)
Hospital discharge	7/184 (3.8%)	0/179 (0%)	0.008	

CI: confidence interval; ROSC: return of spontaneous circulation

There were no statistically significant between-group differences with regards to cerebral performance in the analysis of all patients, or in the analysis of patients who received the study drug and subsequent epinephrine(Table 6).

Table 6: Neurological Outcomes in Patients from Wenzel et al.[20]

Cerebral performance among patients at discharge	Vasopressin	Epinephrine	p-value
Good cerebral performance	15/46 (32.6%)	16/46 (34.8%)	0.99
Moderate cerebral disability	7/46 (15.2%)	12/46 (26.1%)	0.30
Severe cerebral disability	9/46 (19.6%)	7/46 (15.2%)	0.78
Coma or vegetative state	15/46 (32.6%)	11/46 (23.9%)	0.49

The authors concluded that effects of vasopressin were similar to those of epinephrine in the management of VF and PEA, but that vasopressin was superior to epinephrine in patients with asystole, and that vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest.

Gueugniaud et al.[22] published an RCT of vasopressin and epinephrine versus epinephrine alone in cardiac arrest patients in 2008. This study was conducted in France and recruited 2956 patients between May 2004 and April 2006. Patients with out-of hospital cardiac arrest presenting with ventricular fibrillation, pulseless electrical activity, or asystole requiring vasopressor therapy during cardiopulmonary resuscitation were included. Patients aged less than 18 years who had successful defibrillation without a vasopressor, or patients who had traumatic cardiac arrest, pregnancy, documented terminal illness, presence of a do-not-resuscitate order, or obvious signs of irreversible cardiac arrest, were excluded. Randomized patients received either 1 mg/ml IV of epinephrine and 40 IU IV vasopressin, or 1 mg/ml IV of epinephrine and saline placebo in separate injections, less than 10 seconds apart. The same combination of study drugs was re-administered if spontaneous circulation was not restored after the first administration of the study drugs. If ROSC was not obtained after an additional 3 minutes, patients in both groups were given open-label epinephrine. The primary endpoint was survival to hospital admission. Secondary endpoints included ROSC, survival to hospital discharge, good neurologic recovery, and 1-year survival. Neurological performance was

assessed at hospital admission by the Glasgow Coma Scale (GCS) whose scores range from 3 to 15 (lower scores indicate poorer outcome), and at hospital discharge according to cerebral performance categories (CPC) (score range from 1: conscious with normal function, to 5: brain dead or dead). The authors also conducted subgroup analyses for each of the primary and secondary outcomes by type of cardiac arrest (ex. witnessed, unwitnessed, with bystander CPR), initial cardiac rhythm, number of injections, time to resuscitation before drug injection, and end-tidal CO2 during ACLS. Sixty-two of the randomized patients were excluded from the analysis, 1442 patients received the combination therapy, and 1452 received epinephrine alone (N=2894). No treatment-related adverse events were reported. Baseline characteristics of the two groups were comparable, with the exception that there were significantly more men in the combination therapy group than women (75.4% versus 71.7%, p=0.03). The average age of patients was 62 years. The initial cardiac rhythm in 83% of patients was asystole. There were no statistically significant differences reported for the primary and secondary outcomes, although a higher proportion of patients on epinephrine had good neurological recovery (CPC1) at hospital discharge (see Table 7).

Table 7: Primary and Secondary Outcomes from Gueugniaud et al.[22]

End point	Combination Treatment (n=1442)	Epinephrine only (n=1452)	Relative Risk of Death (95%CI)	P value
Survival to hospital admission	299(20.7%)	310 (21.3%)	1.01 (0.97-1.05)	0.69
Survival to ROSC	413(28.6%)	428 (29.5%)	1.01 (0.97-1.06)	0.62
Survival to hospital discharge	24/1439 (1.7%)	33/1448 (2.3%)	1.01 (1.00-1.02)	0.24
1-year survival	18/1437 (1.3%)	30/1447 (2.1%)	1.01 (1.00-1.02)	0.09
Good neurological recovery at hospital discharge	9/24 (37.5%)	17/33 (51.5%)	1.29 (0.81-2.06)	0.29

CI: confidence interval; ROSC: return of spontaneous circulation

No significant between-group differences were found in the subgroup analyses. The authors noted their overall low survival rate compared with previous studies[20] and explained it by the relatively low rate of VF patients in their trial. The authors concluded that the combination of vasopressin and epinephrine does not improve outcomes in cardiac arrest, compared with epinephrine alone.

Observational studies

Mally et al. published an observational study of the effects of epinephrine and vasopressin on end-tidal carbon dioxide tension (pet_{CO2}) and mean arterial blood pressure (MAP) in out-of-hospital CPR in 2007.[23] The aim was to compare the values of pet_{CO2} and MAP in patients with cardiac arrest, and to demonstrate that vasopressin contributes to higher pet_{CO2} and MAP values, consequently leading to better patient outcomes. Data were collected prospectively from a population of 200,000 patients in Maribor, Slovenia from January 2000 to April 2006. All emergency calls that were classified as out-of-hospital cardiac arrest in persons 18 years of age or older and that were dispatched to a pre-hospital emergency unit were included. Patients with a documented terminal illness, successful defibrillation without administration of a vasopressor, or severe hypothermia were excluded. Patients received either 1 mg IV epinephrine every three minutes, or 40 IU IV vasopressin, followed by 1 mg IV epinephrine every three minutes during CPR. Patient allocation to treatment into the two groups was dependent on year of incident (vasopressin became first-line therapy in VF in November 2003, and in asystole in January 2005), and accessibility of vasopressin. Hospital records were used for assessment of

outcomes, including CPC, and discharge status. Univariate and multivariate analyses were performed. A total of 636 cases were identified, 38 of which were excluded because of successful defibrillation without a vasopressor. Of the remaining 598 patients, 452 received epinephrine and 146 received vasopressin first-line. The average age of patients was 62 years and 66% were male. Average pet_{CO2} and MAP values were higher in the vasopressin group. Neurological outcome was better (CPC1 and CPC2) in the vasopressin group (72% of survivors) compared with the epinephrine group (52% of survivors; p=0.04). Among the variables considered in multivariable logistic regression analyses were: shockable rhythm, arrival time, witnessed arrest, bystander CPR, initial $pet_{CO2,}$ average $pet_{CO2,}$ final pet_{CO2}, initial MAP, final MAP, vasopressin, and time period in which CPR was performed. Vasopressin was an independent significant predictor of ROSC and hospital admission (Odds Ratio=1.63 [95%CI: 1.24-2.14], p=0.12), survival at 24 hours (Odds Ratio=1.34 [95% CI: 1.14-1.94], p=0.024), but not of hospital discharge alive (Odds Ratio=1.12 [95% CI: 0.82-1.33], p=0.42). The authors concluded that pet_{CO2} and MAP are strong predictors for the outcome of out-of-hospital cardiac arrest, that patients treated with vasopressin and epinephrine compared with epinephrine alone have higher pet_{CO2} and MAP values on hospital admission, and that this treatment combination improves ROSC, short-term survival, and neurological outcome.

Limitations

There are a limited number of studies evaluating vasopressin compared with epinephrine alone as first line therapy in cardiac arrest.

Very few new studies met the inclusion criteria for this report in the three years since guidelines were last updated. There appeared to be little new evidence to challenge the position of international guidelines on the relative effectiveness of vasopressors in cardiac arrest.

There is some question regarding the relevance of the clinical endpoints chosen in clinical trials,[9,24] and better evaluation of more relevant endpoints such as survival to hospital discharge may require significantly larger sample sizes.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

At the present time, there does not appear to be additional evidence to support the use of a specific vasopressor as first line therapy during human cardiac arrest. Most of the guidelines reviewed for this report considered the meta-analysis by Aung and Htay [21] and the RCT by Wenzel et al. [20] in making their recommendations. The RCT published later by Gueugniaud et al.[22] did not provide evidence for the use of vasopressin first line.

Several authors have brought attention to the somewhat poorer neurological outcomes among patients administered vasopressin in the study by Wenzel et al.[25-27] While poor neurological outcomes among patients administered vasopressin were also slightly more frequent in Gueugniaud et al.,[22] poorer neurological outcomes among surviving patients who are given vasopressin has not been demonstrated to date.

The superiority of vasopressin compared with epinephrine in asystole patients reported by Wenzel et al.[20] was not confirmed by Gueugniaud et al.[22]

Other randomized studies that compared vasopressin with epinephrine were reported in the literature but were not included in this summary because they did not clearly evaluate vasopressin as a first line agent. An American RCT of 325 patients reported by Callaway et al.[28]

administered vasopressin second-line to one group of patients after epinephrine was administered first-line to both groups, also did not find any between-group differences in patient outcomes. Another RCT of 100 patients[29] compared 20 IU vasopressin plus 1 mg epinephrine for up to 5 resuscitation cycles to saline placebo plus 1 mg epinephrine for up to 5 resuscitation cycles, however the vasopressin group also received a corticosteroid during the first cycle. Better ROSC and survival to hospital discharge were reported in the vasopressin group, however it is difficult to ascertain the extent to which this outcome was attributable to the addition of corticosteroids.

Information from ongoing and future trials[30] may provide additional evidence about the clinical-effectiveness of vasopressin over epinephrine for cardiac arrest patients. In the interim, the decision to use one vasopressor over another may be dependent on clinical opinion and possibly cost.

PREPARED BY:
Eva Tsakonas, BA, MSc, Consultant
Carolyn Spry, BSc, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439

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