Atrial natriuretic peptide

Condition: acute kidney injury (AKI)
Intervention: atrial natriuretic peptide (ANP)
Clinical question: Does ANP reduce AKI, the need for dialysis or mortality with AKI? Is it safe?

AKI is common, occurring in 30/1000 hospital discharges and 6% of ICU patients and is still associated with high mortality despite advances in treatment. AKI can be defined using the RIFLE criteria which uses absolute or percentage increase in serum creatinine or reduction in urine output. The aetiology of AKI can be pre-renal, intrinsic-renal or post-renal. In the community, pre-renal failure accounts for 70% of AKI whereas in hospital the predominant cause is intrinsic damage such as obstruction to renal tubules, or ischaemia-reperfusion injury. ANP is produced in atrial myocytes. In the early phase of AKI, ANP causes vasodilatation on the pre-glomerular artery, inhibits prostaglandin release and the renin-angiotensin axis, and later it demonstrates a natriuretic effect which may minimise tubular obstruction. ANP is known to improve GFR from animal studies; however human studies have shown conflicting results.

Review characteristics

- **Eligibility criteria:** RCTs or quasi-randomised RCTs comparing any form or dose of ANP with placebo or active treatment
- **Exclusions:** patients on RRT, those with renal transplants, post renal causes of AKI and those on ANP for other reasons
- **Number of studies:** 19 studies – 11 studies of prevention of AKI and 8 studies of treatment of AKI. 14 of these evaluated patients post major surgery (cardiac, aortic, abdominal)
- **Number of patients:** a total of 1861–1818 in prevention studies and 1,043 in treatment studies
- **Population:** patients at risk of or with AKI
- **Study dates:** 1994–2007

Definitions

- **AKI** = Modified Acute Kidney Injury Network criteria. An abrupt (within 48 hours) reduction of kidney function- increase serum creatinine 0.3 mg/dl or more; 50% or more increase from baseline or 50% or more decrease in creatinine clearance that results in RRT
- **At Risk patients:** those undergoing procedures e.g. with radiocontrast or major surgery associated with AKI
- **Intervention:** any dose of ANP given by any route before or immediately after development of AKI
- **High dose ANP:** studies using > 100 ng/kg/min as this is associated with reduction in MAP, RBF and GFR
- **Active control:** use of other intervention such as furosemide or mannitol

Results

Primary outcomes in studies assessing prevention of AKI

Mortality during hospitalisation or at 30 days: no difference in low-dose ANP group; no mortality events in high-dose ANP study in either intervention group or control.

Need for RRT: lower in low dose but not high-dose ANP group. This effect was not seen when active and placebo controlled groups were analysed separately.

Outcomes	Trials	N	RR	95% CI	I^2
Mortality in low dose ANP group	10	794	0.69	0.21–2.23	0%
RRT in low ANP Group	10	794	0.32	0.14–0.71	0%

Primary outcomes in studies assessing treatment of AKI

Mortality was 35% with no significant difference between ANP and control in low or high dose studies.

Need for RRT: Overall need for RRT was 48% which was lower in the low dose but not high dose ANP group. This effect is also seen with ANP compared to active control but not placebo control.

Outcome	Trials	N	RR	95% CI	I^2
Mortality in low dose ANP group	6	290	0.78	0.41–1.49	36%
RRT in low dose ANP group	6	290	0.54	0.30–0.98	50%

Secondary outcomes in studies

	Studies of prevention of AKI		Studies of treatment of AKI	
Outcome	Trials/N	Results	Trials/N	Results
Hospital LOS	3/201	lower in low dose ANP	NA	NA
ICU LOS	4/219	lower in low dose ANP	1/59	SS in low dose ANP gp
Change in SCr	2/57	No difference	NA	NA
Hypotension	–	No difference	3/813	Higher in high dose ANP gp (I^2 = 72%)
Arrhythmia	1/124	less AF, VE & VT in low dose ANP	2/726	Higher in high dose gp

Subgroup analysis

- **Major surgery**: no difference in mortality; reduction in RRT in prevention but not in treatment studies
- **Radiocontrast nephropathy**: no difference
- **Sensitivity Analysis**: confirmed findings but the reduction in RRT with low-dose ANP was NSS here

Author's conclusion

There aren't enough large, high quality studies to make conclusions regarding the efficacy of ANP however, when used for prevention of AKI in low dose (50–100 ng/kg/min), ANP is well tolerated and may improve some clinical outcomes such as RRT, hospital and ICU LOS. This effect may be most beneficial in patients undergoing major surgery as the time of kidney injury is often known.

Problems & limitations

- The timing of initiation of ANP varied greatly between studies e.g. 2 hours to 7 days in treatment studies
- In most "prevention" studies, definitions of AKI were not given and only severe AKI requiring RRT was reported

Advantages

- Systematic search and methodology

Expert opinion

Eric Hoste

How valid and robust are the data?
This meta-analysis includes 19 studies and 1,861 participants, which would permit strong conclusions if the studies were homogeneous in design. However, there is variation between studies regarding indication for therapy (prevention of AKI and therapy of AKI), study cohorts (cardiac surgery, general ICU etc.), and dose of ANP. Consequently, the results are analysed in several subgroups, such as prevention and therapy of AKI, and high dose and low dose. In addition, there are too few large and high quality studies present.

The data have therefore limited robustness and validity.

Should clinical practice be influenced by this?
No, the data present so far do not permit a change in practice in favour of the use of ANP.

What is the next step?
In contrast to high-dose ANP treatment, low-dose ANP was well tolerated. The data also suggested a beneficial effect of ANP for prevention of development of severe AKI, defined by need for renal replacement therapy (RRT), after cardiac surgery.

Therefore, the potential beneficial effects of ANP should best be further explored in a study aimed at prevention of AKI. This study should be adequately powered and in cardiac surgery patients, comparing a low dose ANP versus placebo. This study should evaluate occurrence of AKI defined by the current sensitive AKI/RIFLE classification, as this is a more sensitive and objective endpoint than initiation of RRT.

Citation

Nigwekar SU, Navaneethan SD, Parikh CR, Hix JK. Atrial natriuretic peptide for preventing and treating acute kidney injury. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD006028. DOI: 10.1002/14651858.CD006028.pub2.

AMSTAR: methodological quality of the review

1.	Was “a priori” design provided?	Y
2.	Was study selection and data extraction adequate?	Y
3.	Was the literature search comprehensive?	Y
4.	Was ‘Grey Literature’ used?	Y
5.	Was a list of excluded studies provided?	Y
6.	Where the characteristics of included studies provided?	Y
7.	Was the scientific quality of studies assessed & documented?	Y
8.	Was the scientific quality of studies weighted appropriately in forming conclusions?	Y
9.	Were the methods used for data synthesis appropriate?	Y
10.	Was the potential for publication bias assessed?	Y
11.	Were any conflicts of interest stated?	Y

Overall quality of trials included	Mostly low
Overall quality of the review	High

Hydroxyethyl starch (1)

Condition: acute kidney injury (AKI)

Intervention: hydroxyethyl starch (HES) solutions

Clinical questions: Does HES have a detrimental effect on renal function compared with other fluid therapies when used in the prevention and treatment of relative intravascular depletion?

Does HES have different renal effects in different ICU populations?

Do the molecular characteristics or amount of HES make any difference?

AKI occurs in up to 30% of critically ill patients and is associated with increases in mortality proportional to the degree of kidney injury. The aetiology of renal damage is often multifactorial although volume depletion leading to hypo-perfusion is a common cause. Intravenous volume replacement remains the main therapy to restore renal perfusion and prevent kidney injury. Starch solutions have duration of action and efficacy as volume expanders, that surpass that of other synthetic colloids except for some dextrans: however they have a tendency to accumulate in the tissues. Starch solutions have been associated with renal damage although the mechanism by which this occurs is poorly understood and a definite survival disadvantage has not been demonstrated.

Review characteristics

- **Eligibility:** RCTs and Quasi-randomised trials comparing HES to another intravenous (iv) fluid
- **Exclusions:** crossover studies & cluster RCTs. Healthy volunteers or euvolaemic patients
- **Number of studies:** 34
- **Number of patients:** 2,577 (median 56, only 1 study had more than 150)
- **Population:** all ages, in a variety of peri-operative and critical care settings, most without pre-existing kidney disease
- **Study dates:** 1982–2008

Definitions

- **HES:** all types; mostly 6% 130/0.4, 200/0.5 and 200/0.6
- **IV fluids:** all types including blood products (but not synthetic blood products)
- **Renal failure:** author defined
- **RIFLE:** Criteria were worked out from individual patient serum creatinine levels where provided by the study authors

Results

Primary outcomes: effects according to various definitions of AKI and various populations

Outcome	Trials	N	RR	95% CI	GRADE
RRT – overall	12	1236	1.38	0.89–2.16	–
RRT in sepsis group	3	702	1.59	1.2–2.1	High
RRT in non-sepsis group	8	487	0.44	0.14–1.38	Moderate
Renal failure – overall	9	1199	1.5	1.2–1.87	–
Renal failure in sepsis group	4	832	1.55	1.22–1.96	Moderate
Renal failure in non-sepsis gp	5	367	1.13	0.57–2.25	Low

Sepsis Group	Trials	N	RR	95% CI	GRADE
RIFLE: risk	2	140	1.28	0.81–2.02	High
RIFLE: injury	2	140	1.39	0.84–2.3	High
RIFLE: failure	2	140	1.45	0.8–2.64	High
Non-sepsis group	**Trials**	**N**	**RR**	**95% CI**	**GRADE**
RIFLE: risk	2	185	0.88	0.27–2.85	Moderate
RIFLE: injury	2	185	0.81	0.12–5.4	Moderate
RIFLE: failure	2	185	0.49	0.07–3.73	Moderate

Secondary outcomes

Mean serum creatinine and creatinine clearance showed no significant difference.

No difference was found between different MW HES solutions however these studies were underpowered and generally lacked outcome data.

Author's conclusion

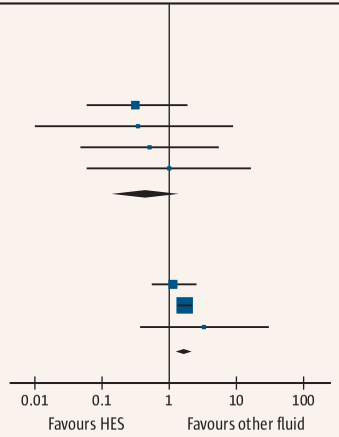
This review shows an overall increased risk of renal failure (as defined by original study authors) in the HES group, as well as a non-significant risk of requiring RRT. Subgroup analysis showed that septic patients treated with HES had a 55% increased risk of developing renal failure and 59% increased risk of requiring dialysis. In non-septic (trauma/surgery) patients there were no significant differences however these studies lacked statistical power due to small participant numbers and low event rates.

There were insufficient data to fully evaluate different HES products.

Fig. 1 Comparison 1 HES versus other fluid, Outcome 1 Renal replacement therapy [from Dart AB, Mutter TC, Ruth CA, Taback SP. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007594, © Cochrane Collaboration, reproduced with permission]

Review: Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function
Comparison: 1 HES versus other fluid
Outcome: 1 Renal replacement therapy

Study or subgroup		HES n/N	Other fluid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1 Non-sepsis	Kumle 1999	0/40	0/20		0.0 [0.0, 0.0]
	Boldt 2007a	0/25	0/25		0.0 [0.0, 0.0]
	Boldt 2003	0/20	0/20		0.0 [0.0, 0.0]
	Boldt 2006	0/25	0/25		0.0 [0.0, 0.0]
	Mahmood 2007	2/42	3/20		0.32 [0.06, 1.75]
	Godet 2008	0/32	1/33		0.34 [0.01, 8.13]
	Boldt 2008	1/30	2/30		0.50 [0.05, 5.22]
	London 1989	1/50	1/50		1.00 [0.06, 15.55]
	Subtotal (95% CI)	**264**	**223**		**0.44 [0.14, 1.38]**
	Total events: 4 (HES), 7 (Other fluid)				
	Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 3 (P = 0.91); $I^2 = 0.0\%$				
	Test for overall effect: Z = 1.41 (P = 0.16)				
2 Sepsis	Schortgen 2001	13/65	11/64		1.16 [0.56, 2.40]
	Brunkhorst 2008	81/261	51/272		1.66 [1.22, 2.25]
	McIntyre 2008	3/19	1/21		3.32 [0.38, 29.23]
	Subtotal (95% CI)	**345**	**357**		**1.59 [1.20, 2.10]**



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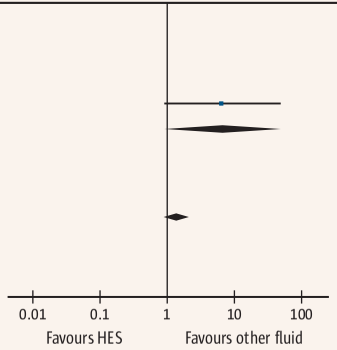
Study or subgroup	HES n/N	Other fluid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Total events: 97 (HES), 63 (Other fluid)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.22$, df = 2 (P = 0.54); $I^2 = 0.0\%$				
Test for overall effect: Z = 3.24 (P = 0.0012)				
3 Deceased organ donor				
Cittanova 1996	9/27	1/20		6.67 [0.92, 48.45]
Subtotal (95% CI)	**27**	**20**		**6.67 [0.92, 48.45]**
Total events: 9 (HES), 1 (Other fluid)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.87 (P = 0.061)				
Total (95% CI)	**636**	**600**		**1.38 [0.89, 2.16]**
Total events: 110 (HES), 71 (Other fluid)				
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 8.48$, df = 7 (P = 0.29); $I^2 = 17\%$				
Test for overall effect: Z = 1.43 (P = 0.15)				



Problems & limitations

- There was significant clinical heterogeneity due to different populations, fluid regimes and duration
- Mortality data was not consistently available. Renal problems may develop later than the follow-up period in the studies (1 day for many)
- No published studies used the RIFLE format instead used various definitions of acute kidney injury/failure. Use of RIFLE format would have ensured consistency and is validated at predicting outcomes. Varying definitions of kidney failure
- Some studies included peri-operative patients that weren't critically ill. Many of these studies are old and almost none used the more recent starch solutions
- There were problems with reliability of some trials (Boldt)
- One large study of septic patients was responsible for the majority of outcomes (Brunkhorst 2008)

Advantages

- A comprehensive review that even identified studies that had renal complications as secondary outcomes
- Conclusion of this review agrees with previous analyses in that HES may adversely affect renal function particularly in septic patients

Expert opinion

Michael Joannidis

How valid and robust are the data?
The review detected 34 randomized and quasi randomized controlled trials published since 1982. The analysis indicates an increased risk of author defined acute kidney injury and a trend toward increased requirement of RRT by HES, which turned out significant in the predefined subgroup of septic patients. However, findings are compromised by heterogeneity in trial design as well in the HES products investigated. Consequently no statement can be made about differences in effects by different HES products showing various molecular weights.

Should clinical practice be influenced by this?
HES products may have the potential of kidney damage especially in patients with sepsis. Consequently the use of HES cannot be recommended for this patient group. The studies showing the most pronounced detrimental effects for the kidneys, however, used older generation large molecular weight HES.

What's the next step?
Colloids are often necessary in cases of true hypovolaemia. Since newer HES products with lower molecular weight and degree of substitution are claimed to have a better safety profile further randomized controlled trials are urgently warranted to clarify whether this class of HES can be used safely.

Citation

Dart AB, Mutter TC, Ruth CA, Taback SP. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007594. DOI: 10.1002/14651858.CD007594.pub2.

AMSTAR: methodological quality of the review

1.	Was “a priori” design provided?	Y
2.	Was study selection and data extraction adequate?	Y
3.	Was the literature search comprehensive?	Y
4.	Was ‘Grey Literature’ used?	Y
5.	Was a list of excluded studies provided?	Y
6.	Where the characteristics of included studies provided?	Y
7.	Was the scientific quality of studies assessed & documented?	Y
8.	Was the scientific quality of studies weighted appropriately in forming conclusions?	Y
9.	Were the methods used for data synthesis appropriate?	Y
10.	Was the potential for publication bias assessed?	Y
11.	Were any conflicts of interest stated?	Y

	Overall quality of trials included	Moderate
	Overall quality of the review	High

Hydroxyethyl starch (2)

Condition: acute kidney injury (AKI)

Intervention: hydroxyethyl starch (HES) solutions

Clinical question: Does the use of HES for volume resuscitation in critically ill patients adversely affect renal outcomes or mortality?

The pathophysiology of kidney damage associated with the use of HES is poorly understood but may be related to histological changes related to variation in osmotic pressure, "osmotic nephrosis-like lesions". Critically ill patients with sepsis, appear to be particularly vulnerable to the adverse effects of HES on renal function. AKI has been validated as an independent risk factor for long-term morbidity, impaired QOL and mortality.

Review characteristics

- **Eligibility criteria:** RCTs of acute volume resuscitation in critically ill patients comparing HES to other fluids
- **Exclusions:** crossover trials, trials using blood, HES for elective surgery or normovolaemic haemodilation
- **Number of studies:** 22 trials (only 6 are the same as in review by Dart et al.)
- **Number of patients:** 1,865 (range 12–537, median 48)
- **Population:** adult patients admitted to ICU or ED who had an indication for acute fluid resuscitation e.g. hypotension, hypovolaemia (8 trials: severe sepsis or septic shock only, 5 others include septic + trauma patients)
- **Study dates:** 1982–2008

Definitions

- **HES:** all types (6 different molecular weights [MW])
- **Control Fluids:** crystalloids, albumin, gelatines, dextrans
- **AKI:** here is defined by the use of RRT
- **Need for urgent fluid resuscitation varied between trials:** low SBP/MAP, lactate, CVP, PCWP or CI
- **Severe sepsis and septic shock:** not specified