HYDROXYETHYL STARCH 130/0.42 VERSUS RINGER'S ACETATE IN SEVERE SEPSIS

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背景

- Surviving Sepsis Campaign guidelines recommend the use of either colloids or crystalloids.
  - 但是之前二個隨機研究顯示Hydroxyethyl Starch(HES)會導致acute kidney failure
    - 所使用的HES為200 kD, substitution ratio > 0.4
  - 目前所使用的HES為 lower molecular weight和lower substitution ratio (130/0.4)
  - 對於HES (130/0.4)的安全性和效用→?

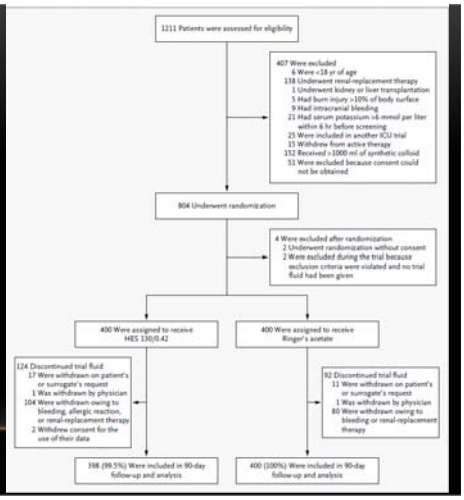
研究目的

- 比較HES(130/0.4)相對於Ringer's acetate對於severe sepsis的病人，是否有較高的死亡率和end-stage kidney failure比率?

研究方法 - I

- 時間:2009/12/23~2011/11/15
- 地點: 26 ICU in 13 university and 13 nonuniversity hospitals (國家： Denmark, Norway, Finland, and Iceland)
- This trial was an investigator-initiated, multicenter, blinded, stratified, parallel-group clinical trial with a computer-generated allocation sequence and centralized, blinded randomization.

研究方法 - II



研究方法 - III

- Maximal dose: 33ml/kg of ideal body weight，超過以Ringer's acetate 代替。
- Outcome:
  - Primary outcome: death or dependence on dialysis 90 days after randomization
  - Secondary outcome: death at 28 days, severe bleeding, SOFA score at day 5, acute kidney injury,

結果 – STUDY POPULATION

Table 1. Baseline Characteristics of the Patients.*

Characteristic	HES 130/0.42 (N = 398)	Ringer's Acetate (N = 400)
Age — yr		
Median	66	67
Interquartile range	56–75	56–76
Male sex — no. (%)	239 (60)	244 (61)
Ideal body weight — kg†		
Median	72	72
Interquartile range	60–80	60–80
Admitted to university hospital — no. (%)	194 (49)	188 (47)
Surgery — no. (%)‡		
Emergency	114 (29)	116 (29)
Elective	34 (9)	48 (12)
Source of ICU admission — no. (%)		
Emergency department	109 (27)	94 (24)
General ward	177 (44)	196 (49)
Operating or recovery room	59 (15)	54 (14)
Other ICU in the same hospital	21 (5)	14 (4)
Other hospital	32 (8)	42 (10)
Source of sepsis — no. (%)§		
Lungs	212 (53)	229 (57)
Abdomen	130 (33)	133 (33)
Urinary tract	56 (14)	50 (12)
Soft tissue	38 (10)	46 (12)
Other	43 (11)	33 (8)
SAPS II — median (interquartile range)¶	50 (40–60)	51 (39–62)
SOFA score — median (interquartile range)‖	7 (5–9)	7 (5–9)
Shock — no. (%)**	336 (84)	337 (84)
Acute kidney injury — no. (%)††	142 (36)	140 (35)
Mechanical ventilation — no. (%)	240 (60)	245 (61)

結果 - FLUID THERAPY BEFORE AND AFTER RANDOMIZATION

Variable	HES 130/0.42 (N = 398)			Ringer's Acetate (N = 400)			P Value†
	Patients	Volume Received‡		Patients	Volume Received‡		
		median	interquartile range		median	interquartile range	
	no./total no.§	ml		no./total no.§	ml		
Trial fluid							
Day 1¶	374/397	1500	1000–1500	375/400	1500	1000–2000	0.09
Day 2	288/379	1500	1000–2000	307/380	1500	950–2000	0.50
Day 3	176/330	1000	500–1500	170/326	1000	500–1500	0.78
Open-label trial fluid							
Day 1¶	157/397	1500	1000–2000	177/400	1500	800–2500	0.21
Day 2	114/379	1000	500–1500	133/380	1000	500–2000	0.13
Day 3	54/329	900	500–1000	57/326	1000	500–1250	0.69
Other fluids‖							
Day −1**	356/366	3500	2000–4938	370/385	3000	2000–4868	0.08
Day 1¶	389/394	2235	1325–3197	393/396	1976	1077–3046	0.12
Day 2	373/376	2980	2143–3960	369/371	2905	2094–3780	0.50
Day 3	313/316	3150	2365–3910	315/317	3035	2183–3924	0.33
Blood products††							
Day −1**	90/392	838	480–1435	88/399	600	490–1195	0.69
Day 1¶	109/397	590	300–1100	89/400	600	490–980	0.13
Day 2	115/378	600	350–1100	78/379	526	300–1030	0.001
Day 3	81/327	500	300–980	68/326	598	300–750	0.28
Total‡‡	243/376	1340	566–2700	204/380	1055	600–2755	0.003

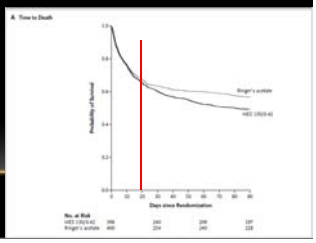
結果 – OUTCOME

Table 3. Primary and Secondary Outcomes.*

Outcome	HES 130/0.42 (N = 398)	Ringer's Acetate (N = 400)	Relative Risk (95% CI)	P Value
Primary outcome				
Dead or dependent on dialysis at day 90 — no. (%)	202 (51)	173 (43)	1.17 (1.01–1.36)	0.01
Dead at day 90 — no. (%)	201 (51)	172 (43)	1.17 (1.01–1.36)	0.01
Dependent on dialysis at day 90 — no. (%)	1 (0.25)	1 (0.25)	—	1.00
Secondary outcome measures				
Dead at day 28 — no. (%)	154 (39)	144 (36)	1.08 (0.90–1.28)	0.43
Severe bleeding — no. (%)†	38 (10)	25 (6)	1.52 (0.94–2.48)	0.09
Severe allergic reaction — no. (%)†	1 (0.25)	0	—	0.32
SOFA score at day 5 — median (interquartile range)	6 (2–11)	6 (0–10)	—	0.64
Use of renal-replacement therapy — no. (%)‡	87 (22)	65 (16)	1.35 (1.01–1.80)	0.04
Use of renal-replacement therapy or renal SOFA score ≥3 — no. (%)§	129 (32)	108 (27)	1.20 (0.97–1.48)	0.10
Doubling of plasma creatinine level — no. (%)†	148 (41)	127 (35)	1.18 (0.98–1.43)	0.08
Acidosis — no. (%)†¶	307 (77)	312 (78)	0.99 (0.92–1.06)	0.72
Alive without renal-replacement therapy — mean % of days‖	91	93	—	0.048
Use of mechanical ventilation — no. (%)†	325 (82)	321 (80)	1.02 (0.95–1.09)	0.61
Alive without mechanical ventilation — mean % of days‖	62	65	—	0.28
Alive and out of hospital — mean % of days‖	29	34	—	0.048

討論 - I

- HES 130/0.42 increased the absolute risk of death at 90 days by 8 % points (number needed to harm: 13)
- The separation of the survival curves occurred around day 20 in both trials → late death induced by HES
  - Impaired coagulatioon
  - Use of RBC ↑
  - HES無法代謝→toxic effect



討論 - II

- Colloid一直被認為有volume expansion 的效果，但是在本研究並觀察到。
- Limitation:
  - 未包含hemodynamic monitoring or cointerventions in the protocol
  - Included patient with acute kidney injury
  - 77個病人給予open-label synthetic colloid (但二組相同)
  - 69個病人給予輸液超過每天最大劑量，但本研究定的劑量低於廠商所建議的量。(只有二個病人超過)

結論

- Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal-replacement therapy, as compared with those receiving Ringer's acetate.