

Effects of Intravenous Fluid Restriction on Postoperative Complications: Comparison of Two Perioperative Fluid Regimens (a RCT)

Brandstrup et al

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Dogmas / Standards?

- Large tidal volumes / no PEEP
- "Renal" Dopamine
- Lasix drips to treat / prevent renal failure
- Normal Saline (crystalloids)
- PA catheters periop / sepsis
- Total Parenteral Nutrition
- "Stress dose" steroids
- Calcium channel blockers / short acting beta blockers to prevent myocardial ischemia
- Sodium bicarbonate for lactic acidosis
- Lorazepam infusions for ICU sedation



The Onus of Proof is
ALWAYS on the intervention!



Question/Hypothesis

- Does a "restrictive" perioperative intravenous fluid regimen reduce postoperative complications compared to "standard" therapy?



Background

- Current perioperative fluid administration and replacement strategies are based on anecdote, supposition and opinion



Lobo et al

- 20 patients undergoing lower GI surgery were randomized to standard IVF or fluid restriction
- >3kg weight gain from fluid significantly delayed the return of GI function and prolonged hospital stay



Design

- Prospective
- Randomized
- Observer blinded
- Multi-center (8 Danish Hospitals)
- Controlled trial



Setting

- In what environment was the study carried out?
- Academic medical centers



Methodology



Methodology

- Who was enrolled and what were the criteria?
- Inclusion criteria
 - Adult patients for elective colorectal resection (ASA 1-3)
 - Presence of both the investigating anesthesiologist and surgeon
 - Minimum of 16 patients from each center



Methodology

- Who was not and what were the criteria?
- Exclusion criteria
 - Pregnancy, lactation, mental disorders, language problems, alcohol >35units/week, diabetes, renal insufficiency, disseminated cancer, IBD, secondary cancers, diseases hindering epidural placement
 - Would any of our patients make it into this study?



Randomization

- If the study was randomized, how was this achieved?
- Sealed envelopes, computer generated sequence
- Two errors identified



TABLE 2. Baseline Characteristics, Surgical Procedures, and Risk Factors

		Restricted Group (n = 69)	Standard Group (n = 72)
Sex	Male/female (n)	33/36	37/35
Age	Years median (range)	64 (42-90)	69 (41-88)
Body mass index	Median (range)	25 (12-38)	25 (18-33)
ASA classification*	ASA 1 (n)	34 (49%)	32 (45%)
	ASA 2 (n)	33 (48%)	39 (54%)
	ASA 3 (n)	2 (3%)	1 (1%)
APACHE2 score*	Median (range)	5 (0-14)	6 (0-11)
Smoking habits	Smokers (n)	20 (28%)	29 (40%)
	g/day, median (range)	15 (4-30)	10 (1-48)
Alcohol habits	Cans/day (n)	48 (70%)	44 (61%)
	Drinks/week, median (range)	10 (2-35)	9 (1-25)
Comorbidity	Cardiovascular diseases (n)	25 (36%)	27 (38%)
	Pulmonary diseases (n)	4 (6%)	9 (13%)
	Other diseases (n)	6 (9%)	3 (4%)
Diagnosis	Malignant/benign (n)	50/19	56/16
Surgery	Resections of the colon (n)	36 (52%)	39 (54%)
	Resections including the rectum (n)	33 (48%)	33 (46%)
Anastomosis	Ileo-colo-colo-colo (n)	19/14 (1 with stoma)	7/26
	Ileo-rectal or -sami-colo-rectal (n)	3/19 (6 with stoma)	1/21 (3 with stoma)
Duration of surgery	Hours, median (range)	3 (1.5-6.0)	3 (2.0-6.5)
Blood loss	Median (range) (mL)	400 (0-4530)	500 (0-1600)
Blood transfusions	Transfused during hospital stay (n)	19 (28%)	20 (28%)
Enteral nutrition by tube	Median (range) (mL)	600 (264-2400)	675 (300-5400)
	Patients without tube (n)	7 (10%)	10 (14%)
	Day of surgery (mL) median (range)	500 (60-930)	500 (10-800)
	1 Postoperative day (mL)	775 (0-1100)	740 (0-1200)
	2 Postoperative day (mL)	500 (0-1250)	500 (0-1200)
	3 Postoperative day (mL)	225 (0-1285)	325 (0-1100)

*American Society of Anesthesiologists physical scoring system.
 *Acute Physiology And Chronic Health Evaluation²

Statistical Analysis

- Did the authors perform a power analysis?
- Yes – 140 patients required to detect a reduction in complication frequency by 20%
- How was the data analyzed?
- X², Fisher exact test, Student's T, Mann Whitney U test



Interventions

TABLE 1. Intraoperative Fluid Therapy

	Restricted Regimen	Standard Regimen
Preloading of epidural analgesia	No preloading.	500 mL HAES 0%.*
Third space loss	No replacement	Normal saline 0.9%; 7 mL/kg/h first hour; 5 mL/kg/h second and third hour; 3 mL/kg/h following hours.
loss during fast (maintenance)	500 mL of glucose 5% in water less oral fluid intake during fast.	500 mL of normal saline 0.9% independent of oral intake.
Blood loss	Volume-to-volume with HAES 6% with allowance for max. 500 mL extra.	Loss up to 500 mL: 1000-1500 mL of normal saline; Loss >500 mL, additional HAES 6%.
	Blood component therapy started at approximate loss >1500 mL dependent on hematocrit.	Blood component therapy started at approximate loss >1500 mL dependent on hematocrit.

*Hydroxyethyl starch 6% in normal saline.

Maximal HES 33/mL/Kg -> 5% albumin
 MAP maintained with ephedrine / dopamine



Standardization

- All patients could drink clear fluid until 2 hours pre-op
 - The patients did not have fasting fluid deficit!
- Epidural analgesia / standard anesthetic
- Naso-enteric feeding tube
 - Early enteral and oral feeding from 4 hours
 - 500ml day of surgery, 1000ml thereafter
- Multimodal analgesia



Main Outcome Measure

- The primary outcome was complications registered 30 days post-operative.
 - Assessment registered unblinded, reassessed by 3 blinded surgeons
- Secondary outcomes:
 - Death and adverse effects, including impairment of renal function and postoperative hypotensive episodes



Data Collection

- Fluid loss and administration were registered from the beginning of fasting to the sixth postoperative day.
- The patients were weighed on admission, on the morning of operation, and every morning on the subsequent 6 days.
- Physiological changes were monitored both intraoperatively and postoperatively, arterial blood was sampled by protocol and by demand
- Venous blood was sampled daily until discharge or the sixth postoperative day.



Critical Appraisal of the Methodology

Appraisal of Methodology

- Were the patients properly randomized?
 - Yes
- Were the groups comparable?
 - Yes
- Was the outcome assessment "blind"?
 - Yes
- Was the study large enough?
 - Yes

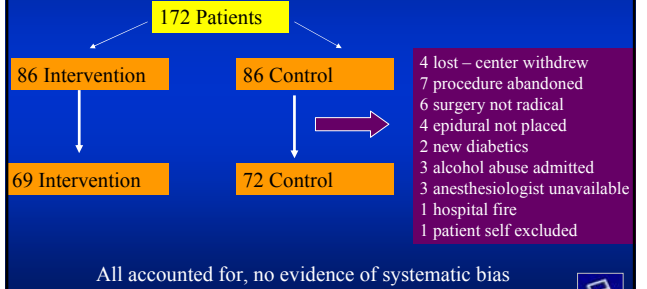


Appraisal of Methodology

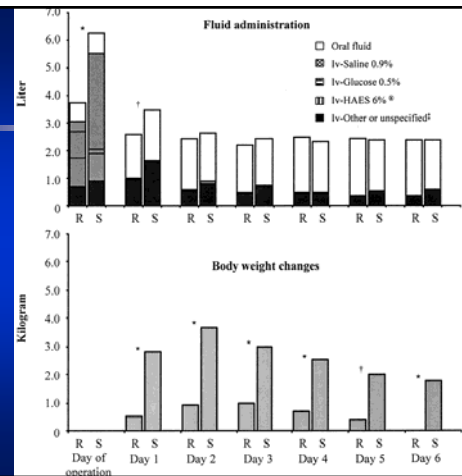
- Was the study length sufficient?
 - Yes
- Was it stopped after an interval evaluation?
 - No, but interval evaluation performed
- Was the follow up complete – were all the patients who entered the trial accounted for at its conclusion?
 - Yes
- And were they analyzed in the groups into which they were randomized?
 - Yes

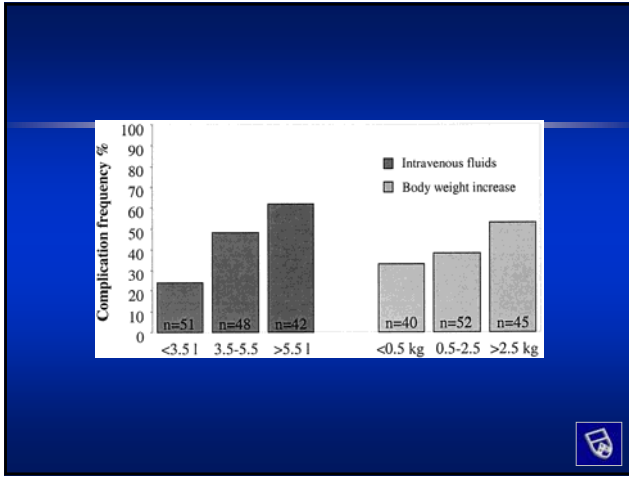


Patient Distribution



Results





- ## Results Primary Endpoint
- Patients in the standard group received significantly more fluid, and gained more weight over days 1 and 2 than in the restricted group
 - Median fluid – 5388ml vs 2740 p<0.0005 (similar volumes of HES) (1000 ml difference first POD)
 - 15% of patients in R group got more fluid than planned, 24% of patients in the S group got less fluid than planned

- ## Results Primary Endpoint
- On intention to treat basis
 - 28 (33%) patients in R group had complications vs 44 (51%) in the S group p = 0.013
 - ARR overall 18%, NNT 5.5
 - Major complications NNT 7
 - Minor complications NNT 4
 - Tissue healing comps 7
 - Cardiopulmonary comps 6

TABLE 3. Number of Patients With Complications (Per-Protocol Analysis)

	Blinded Assessment			Unblinded Assessment		
	Restricted Group	Standard Group	P value	Restricted Group	Standard Group	P value
Overall complications	21	40	0.003	21	43	0.000
Major complications*	8	18	0.040	8	19	0.026
Minor complications*	15	36	0.000	15	37	0.000
tissue-healing complications*	11	22	0.040	10	24	0.009
cardiopulmonary complications*	5	17	0.007	4	18	0.002

n = 69 in restricted group and n = 72 in standard group.
*Number of patients in subgroups does not add up to number of overall complications because some patients had more than 1 complication.

TABLE 4. Requirements for Acceptance of Complications and Total number of Complications Registered by Blinded Assessment

Major Complications	Requirements for Acceptance	Restricted Group (n = 49)	Standard Group (n = 72)
Anastomotic leakage ^a	Requiring operation	1	4
Leakage of the rectum ^b	Drained deep abscess	2 ^c	2
Fistulas without leakage	Operation (evidence of anastomotic leakage)	1	0
Sepsis	Positive blood culture +/- DIC ^d or multi organ dysfunction	0	4
Necrosis of stoma ^e	Intra-peritoneal necrosis requiring operation	1	0
Wound dehiscence ^f	Suture of the fascia	1	1
Intestinal obstruction	Requiring operation	2	2
Bleeding	Requiring transfusions and surgical treatment	1	5
Stroke	Clinical symptoms and radiographic changes	0	2
Pulmonary emboli ^g	Causing sudden death or isoelectric changes	0	1
Pulmonary edema ^h	Needing assisted ventilation	0	4
Myocardial infarction ⁱ	EKG changes and myocardial enzyme elevation	0	0
Ventricular arrhythmias ^j	EKG changes, medical treatment, and/or electro conversion	0	2
Bradycardia ^k	Heart rate <50, medical treatment, and/or pacing	0	4
Renal failure	Requiring dialysis	0	1
Lesion of the ureter	Uretery extravasation requiring operation	1	1
Minor Complications			
Superficial wound infection, hematoma, or dehiscence ^l	Surgical evacuation of pus or hematoma, secondary suture and/or prolonged nursing care	9	18
Paralytic ileus	>7 days without flatus	1	0
Pulmonary congestion ^m	Shortness of breath, crepitation, and medical treatment	2	8
Pneumonia ⁿ	Elevated temperature and radiographic changes	3	9
Pleurothorax	Requiring drainage	0	1
Minor cardiac arrhythmias ^o	EKG changes, medical treatment, and/or electro conversion	0	7
Dysrithm	Elevated temperature, dysrithm, and positive culture	1	5
Postoperative headache	Requiring blood patch	0	1
Psychosis	Delusions and medical treatment	0	1
Total		26	83
Number of complications per patient with complications (n)		1,2 ^p	2,1 ^q

^aAccepted following reoperation for anastomotic leakage respective necrosis of stoma.
^bAccepted in situ.
^cAccepted in situ.
^dAccepted as disseminated intravascular coagulation.
^eAccepted as tissue-healing complications.
^fAccepted as anastomotic complications.



Results Secondary Endpoints

- No ss difference in:
 - Mortality
 - Postoperative hypotension
 - Renal failure
- What about length of hospital stay or medically fit for discharge?



Questions about results

- Information about perioperative pressor use?
- No biochemical information given – could this be explained by hyperchloremia?
- Amount of albumin administered not available
- Use of glucose 5% is curious



Conclusions



Authors Conclusions

- The restricted perioperative intravenous fluid regimen aiming at unchanged body weight reduces complications after elective colorectal resection.



Validity of results

- Are the results valid?
- Is this a study of fluid restriction or of early enteral nutrition?
- Would the results have been different if patients were fasted pre and post op?
- Did the electrolyte content of infused fluids influence outcome?
 - Would the results be the same with Normisol or LR?



Implications for Practice

- We probably over treat patients with isotonic crystalloids, intra and post op
- However, this was a study of a single operation (colectomy)
- Involving:
 - Liberal HESPAN administration
 - Minimal fluid fasting
 - Early enteral nutrition
 - Multimodal analgesia
- Do we do this at PENN?



Comments

