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Format for ANSWERING REVIEWERS



August 25, 2012

Dear Editor,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Perioperative restricted fluid therapy preserved immunological function for patients with colorectal cancer" (ESPS Manuscript NO: 10629). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The changes are highlighted in red in the revised manuscript. We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Yun-Xiang Li

Title: Perioperative restricted fluid therapy preserved immunological function for patients with colorectal cancer

Author: Jie HY, Ye JL, Zhou HH, Li YX.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 10629



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Reviewer 1

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

Response: We believe that the language of this manuscript has reached Grade A and would like to sign a guarantee.

COMMENTS TO AUTHORS

1. The authors have done a randomized trial comparing the outcome and markers for immunologic function between a restricted and a normal preoperative therapy. It is a interesting theme and a interesting article, but I am not able to understand what the difference between the two group of fluid therapy is. Also I miss in the introduction a better rationale behind picking the CD4/CD8 ratio and Treg, explaining what these factors mean. In the discussion I miss a more thorough discussion of the immunologic markers, and possible weaknesses of the study

Response: Thank you very much for your good suggestion, we have improved two group of fluid therapy in the table 1. In addition, we have also added the rationale of CD4/CD8 ratio and Treg in the introduction. It was previously reported that colorectal cancer patients with advanced disease have reduced numbers of CD4+ T cells leading to a decreased CD4:CD8 ratio. Th1, Th17 and Treg cells represent three CD4+ T-cell subsets that share important developmental elements, but ultimately bifurcate into distinct phenotypes with remarkably opposite activities, Th1 and Th17 cells being pro-inflammatory, and Tregs being anti-inflammatory. Treg are a small subset of CD4+ T lymphocytes (about 5%) which suppress functions of autologous conventional T cells, which are positively correlated with effectors T-cells, and the activity of all these effector T cells is attenuated by the anti-inflammatory action of regulatory T cells (Tregs) that inhibit T-cell proliferation and T-effector function. These cells are critical for the prevention of excessive immune activation and autoimmune responses perpetrated by self-reactive T cells. In the discussion we have also discussed the meaning of immunologic markers.

Table 1 Perioperative fluid regimens

Perioperative period	Restricted fluid	Standard fluid
Preloading of epidural	No preloading	500 mL 6% HAES



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analgesia		
During the operation	7 mL/kg RL in first hour; 5 mL/kg/h RL in following hours	12 mL/kg/h RL
Remainder of the operation day	1,000 mL 5% glucose (with potassium if needed)	12 mL/kg/h RL
Days following operation	1,000–1,500 mL crystalloida	2,000–2,500 mL crystalloid

Reviewer 2

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

Response: We believe that the language of this manuscript has reached Grade A and would like to sign a guarantee.

COMMENTS TO AUTHORS

1. This is a randomized prospective trial examining perioperative fluid restriction on the effect of CD4/CD8 T lymphocyte ratio and Treg percentage values. As a randomised trial, the recruitment process and documentation was not reported in accordance to the CONSORT statement. The recruitment process was not clearly stated and the number of patients screened for the trial was not reported.

Response: Thank you very much for your good comment, we have added the CONSORT statement as below.

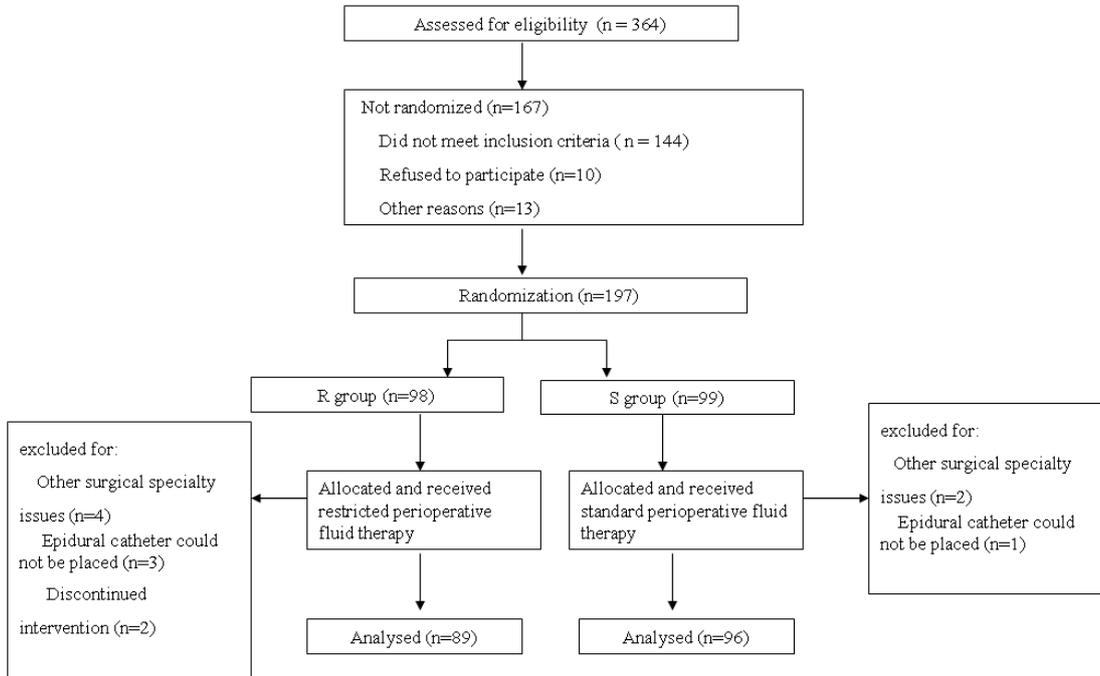


Figure 1 CONSORT diagram for the trial.

Blinding was described. The power analysis and sample size estimation was not reported.

Response: We are very sorry for our negligence of this, before the trial was started, it was estimated that A sample size of 70 patients in each group had a power of 80% to detect an effect size of 1.00 SD using a two-group t-test with a 0.05 two-sided significant level.

There was no mention of a preoperative hydration regime if used and the type of bowel preparation used prior to surgery as this can affect the preoperative hydration status of the patients.

Response: Thank you very much for your good comment. Patients included in this study did not had mechanical bowel preparation, and were allowed to have normal meals. Caroline *et al.*¹ demonstrated that elective colorectal surgery can be safely done without mechanical bowel preparation in a a multicentre randomised trial. In view of possible disadvantages of this practice, patient discomfort, and the absence of clinical value, mechanical bowel preparation before elective colorectal surgery were abandoned in our hospital.

1. Lancet 2007; 370: 2112-17

There was no mention if laparoscopic procedures were used.

Response: Thank you very much for your good suggestion. We have added the type of surgery (laparoscopic vs open) and the P value is 0.38.

Time to flatus and to bowel movement is an important indicator of bowel function recovery and would affect the time for withdrawal of intravenous fluid supplementation. Incidence of ileus should also be reported as an end point. Pre and postoperative body weight monitoring is important.

Response: Thank you very much for your good comment. All patients received 1,000–1,500 mL crystalloid in R group and 2,000–2,500 mL crystalloid in S group. Furthermore, patients were allowed 30 mL/h of oral fluid. Twelve hours later, oral fluids were increased to 60 mL/h, and another 12 h later to unrestricted oral fluid, unless ileus or nausea developed. Patients with ileus only received 1,000–1,500 mL crystalloid in R group and 2,000–2,500 mL crystalloid in S group in this present study. There was no significant difference in time to return of bowel function (passage of flatus) between the restricted and standard groups (2.8 ± 0.8 vs 3.0 ± 0.9 days; $P = 0.11$). In the first 3 days after surgery the median weight gain was smaller in the restricted group (Fig. 3).

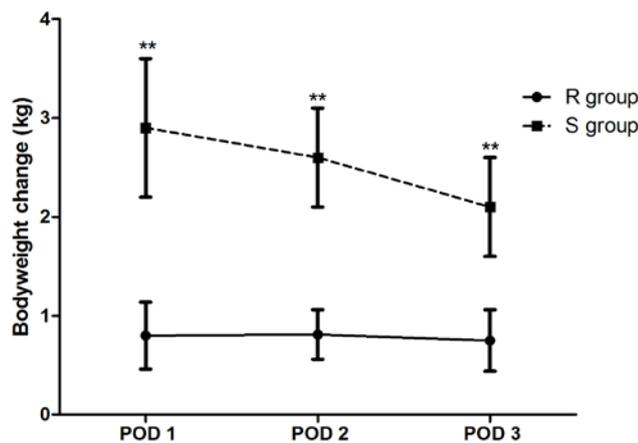


Figure 3 Body weight changes in the first 3 days after surgery in two groups. Data are mean \pm SD. POD, Postoperative day; * $P < 0.05$ and ** $P < 0.01$ between groups.

While there is a quicker recovery in the CD4/CD8 ratios and Treg percentages with restricted fluids, the authors had not shown if the changes account for specifically patient recovery and infection.

Response: Thank you very much for your good comment. Perioperative restricted intravenous fluid regimen results in a low postoperative complication rate and better preservation of cellular immunity (CD4/CD8 ratios and Treg percentages), which at least in part, explains the improved



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clinical outcomes associated with the restricted fluid regimen after surgery for patients with colorectal cancer.

In the discussion section, the significance of the changes in the CD4/CD8 and the Treg percentages were not clinically discussed and their biochemical and clinical significance if any explained. Overall, this is an interesting study and merits further investigations.

Response: Thank you very much for your good comment. A previous study demonstrated an increased CD4/CD8 ratio during the postoperative period in patients with colorectal cancer receiving anti-inflammatory therapy using fish oil. Furthermore, Zhu *et al.* demonstrated that CD4/CD8 ratio to return to normal might indicate recovery of the anti-infection mechanism and may have reduced septic events. Th1, Th17 and Treg cells represent three CD4+ T-cell subsets that share important developmental elements, but ultimately bifurcate into distinct phenotypes with remarkably opposite activities, Th1 and Th17 cells being pro-inflammatory, and Tregs being anti-inflammatory. Tregs are positively correlated with effectors T-cells, and the activity of all these effector T cells is attenuated by the anti-inflammatory action of regulatory T cells. These cells are critical for the prevention of excessive immune activation and autoimmune responses perpetrated by self-reactive T cells.

Special thanks to you for your good comments.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Yun-Xiang Li