

July 26, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Perirenal space blocking restores gastrointestinal dysfunction and improves prognosis of patients with severe acute pancreatitis

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Comments 1. How to randomize the patients need to be clarified.

Reply: Patients were randomly assigned to either perirenal space blocking (PSB) or no perirenal space blocking (NPSB) group. Randomization was performed centrally by the study coordinator. Permuted-block randomization was used with a concealed block size of four. Randomization was stratified according to the treatment center.

Comments 2. GIF only for up to 10 days, while patients can stay beyond 10 days, this may bring selection bias.

Reply: The two critical stages of SAP are as follows: One is the acute reaction stage (i.e., early stage) characterized by SIRS, which normally lasts about 10 d, and the other is the infection stage immediately after the acute state, which is manifested by secondary peripancreatic and pancreatic necrotic tissue infections. Both stages are the peak periods of deaths. During the acute stage of SAP, SIRS causes gastrointestinal dysfunction. This consequence causes intestinal gas, dilatation, and paralysis, which greatly impede enteral nutrition. It also causes bacterial translocation, leading to secondary infections. Nowadays, expectant treatment is the primary treatment method for SAP in clinical practice, and scholars have basically reached a consensus: The higher the operation rate is, the higher the death rate will be. As for expectant treatment, the main clinical managements of acute SAP include vital organ stability maintenance, hydroelectric correction, acid-base balance, infection prevention, and nutritional support. Timely, rational, and effective emergency aid and treatment during the acute stage to reduce the incidence rate of secondary infections or to delay the secondary infection or infectious complications of peripancreatic and pancreatic necrotic tissues can greatly reduce the overall death rate of SAP patients. Once infection or infection associated complications occur, clinical management will become very difficult to exert an

effect and only surgical intervention can achieve some curative effect. Therefore, the adoption of rational treatment methods for early SAP is of great significance for preventing SAP infections. This is also why we selected 10 d for GIF scoring.

Comments 3. The discussion are deviated from clinical findings.

Reply: The discussion of this study was around the topic why renal vesicle (perirenal space) blockage can treat SAP. We started the discussion with “solar plexus” because it is the center of the abdominal organs, which was followed by the anatomic relations of renal vesicles and the pancreas with celiac ganglia and plexuses, as well as the pathophysiological characteristics of pancreatitis. By doing this, we gave a hint foreshadowing the feasibility of the treatment method we used in this study. Then, we moved on with the discussion of the secondary infection rate decreasing effect of enteral nutrition on SAP. However, as gastrointestinal dysfunction occurs during SAP, which is caused the inflammatory stimulation upon the solar plexus, enteral nutrition cannot be satisfactorily realized. We used renal vesicle blockage as the solution to this problem and achieved good results. Furthermore, we compared renal vesicle blockage with other similar techniques and the results showed that this technique has advantages over others. Therefore, we do not think we have deviated from the clinical findings.

Comments 4. The overall mortality data are needed to characterize the significance of this intervention.

Reply: Both the pancreas and the kidneys are located at the retroperitoneal space and are adjacent with each other. Apart from the pancreas and kidneys, this space also contains large and small visceral neural stems as well as abundant visceral ganglia (including celiac ganglia) and plexuses (including solar plexuses, enteric plexuses, and pancreatic plexus). Both the kidney and the adrenal glands are wrapped by renal fascia, which is further dressed by a thick adipose layer outside (the renal vesicle; the average thickness is 2 cm). The posterosuperior part and inside of the space neighbor on the crus of diaphragm, large and small visceral neural stems, and solar ganglia and plexuses and the right and left renal vesicles communicate through an interspace. Among different local anesthetics, lidocaine has the most excellent diffusion and fastest nerve-blocking effects in the tissue space. After a puncture with 1% lidocaine, catheter posterior insertion into the right renal vesicle, and intermittent injection and blockage, the anesthetic can rapidly diffuse to the aforementioned tissue through channels to exert a nerve block effect.

Inflammation diffusion towards the retroperitoneal space is the primary and direct extension pattern in SAP. The leakage out of the pancreas and histolysis of the inflammatory liquids with abundant pancreatin inevitably stimulate splanchnic ganglia and plexuses. They also influence the nervous system governing the gastrointestinal tract during this pathological course, thereby affecting its normal functions. Secondary peripancreatic and

pancreatic necrotic tissue infections during SAP are associated with bacterial translocation caused by gastrointestinal motor dysfunction and enteral dysbacteria, which are the consequences of the simulation upon the splanchnic ganglia and plexuses after the leakage of pancreatin-abundant inflammatory liquids out of the pancreas during early SAP. The results of this study showed that renal vesicle blockage benefited the restoration of gastrointestinal motor functions. This treatment realized early enteral nutrition, strengthened the barrier and immune functions of the intestinal mucosa, corrected enteral dysbacteria, and prevented bacterial translocation, thereby reducing the infection incidence and death rates. In addition, renal blockage blocked the pain transduction of the sympathetic nerves governing the pancreas, thereby rapidly easing violent abdominal pains. This effect helped stabilize SAP patient's pathogenetic conditions, decrease heart and lung burdens, and reduce the incidence rate of associated complications.

We have checked typo and grammatical errors. In addition, we have asked CrossEdit Company to help us to edit the language.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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