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Letter to the Editor

The Evidence of DA-9701 on Bowel Motility

TO THE EDITOR: With great interest we read the paper by Lee et al[1] "effect of DA-9701, a novel prokinetic agent, on post-operative ileus in rats." The main finding seems to be that DA-9701 can ameliorate post-operative ileus (POI) by reducing delayed gastrointestinal transit (GIT) and improving ghrelin levels after surgery in a rat model of POI. Both the Pharbitidis Seed[2] and Corydalis Tuber[3] have been extensively used for centuries as medical herbs respectively in the control of gastrointestinal motility and visceral pain in China. The Chinese Pharmacopoeia says that Pharbitidis, with strong purgative action, resembles Jalapin in chemical properties in aspects of secretion of bile and intestinal juice, which can stimulate and enhance intestinal peristalsis. Corydalis possesses soothing, narcotic, and tranquilizing properties; it is commonly used to alleviate abdominal pains and mild depression, mild mental disorders, emotional disturbances, severe nerve damage, and limb tremors. With the new technological application, both pharbitidis seeds and corydalis extractions were synthesized as one medication named as Motilitone (DA-9701) by Dong-A Pharmaceutical in Korea. It has been a new medication for functional dyspepsia since December 2011 in Korea.[4] As stated by Lee et al,[1] post-operative ileus is a common complication of abdominal surgery, and therefore such a POI rat model is used in the study. The authors provide evaluations about the effect of DA-9701 on bowel motility in a variety of post-operative conditions in rats. Certain parameters indicate that DA-9701 significantly accelerates gastric emptying, increases fecal pellet weights, and elevates ghrelin serum levels. Therefore, it is logically implicated that DA-9701 can prevent or control POI.

There are serval concerns raised in the paper. First, the paper is titled as "Effect of DA-9701, a novel prokinetic agent, on post-operative ileus in rats." What the novelty of the study is when compared to the literature about DA-9701 is this study regarding DA-9701 on POI. Many literatures on DA-9701 have already been acknowledged with its prokinetic effect in gut motility.[4] Whilst, this study is mimic a post-operation ileus (by using minor surgery) to compare the changes of GIT, fecal weight, and ghrelin that are affected by DA-9701.

In the procedures as shown in Figure 1, the acclimatization period for rats was 7 days, and DA-9701 was gavaged once respectively before and after operation, without vehicle or agent as a control. It is unclear why the 7 days acclimatization is necessary without time course scaling comparison; also, it is hard to believe that any effect or change, without a control, resulted from DA-9701 instead of mechanical delivery. A rational explanation needs to be addressed by the authors.

To look up GIT parameters and stool weight as shown in Figure 2, the effect from DA-9701 could be categorized as no surgery/no medication (NSNM) versus no surgery/medication

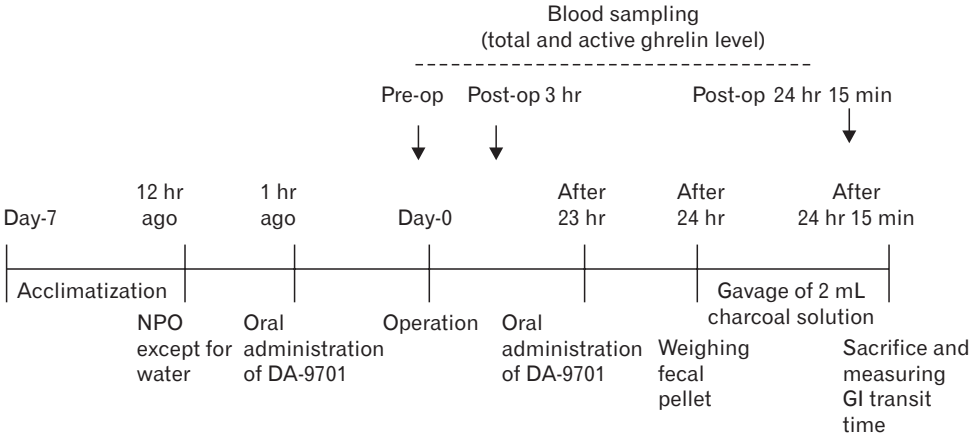

Figure 1. Schematic diagram of the experimental protocol. Pre-op, pre-operative; Post-op, post-operative; NPO, nil per os; GI, gastrointestinal. Reproduced from Lee et al.[1]

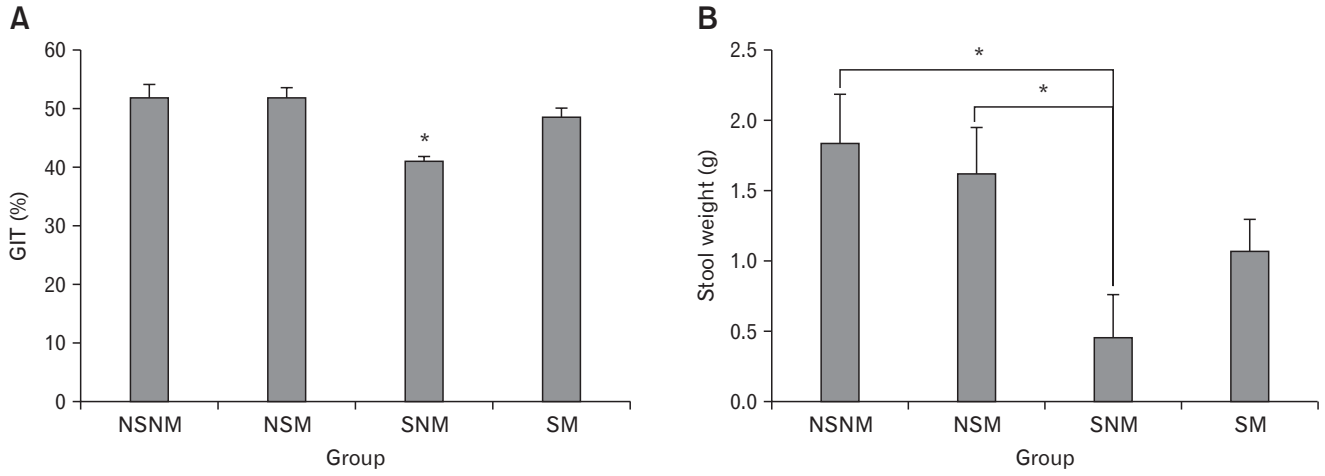

Figure 2. Gastrointestinal transit (%) and cumulative stool weights (g) by group. (A) Gastrointestinal transit (GIT) was significantly delayed in the surgery/no medication (SNM) group compared with the other groups. (B) Cumulative stool weight was significantly lower in the SNM group than in the no surgery/no medication (NSNM) and no surgery/medication (NSM) groups. SM, surgery medication. The asterisk (*) indicates a statistically significant difference. Reproduced from Lee et al.[1]

(NSM), surgery/no medication (SNM) versus surgery/medication (SM). As the results show in Figure 2A there is no change between NSNM and NSM, and significant changes between SNM and SM. We question how to understand DA-9701 selectively effect on SM, but not NSM? In Figure 2B, we are more confused as to why the authors compared between no surgery, and surgery + no medication, especially the critical comparison of SNM and SM is not significantly changed. It suffers from a number of weaknesses in drawing their conclusions.

Active ghrelin levels were used as an indication of POI in the paper. As shown in the Supplementary Figure, ghrelin levels are elevated in the non-surgery group at 24 hours (NSNM vs NSM), unfortunately this was an oversight by the authors. Instead, the authors stated a decrease level found significantly in SNM, but not in SM, and the evidence used claims that DA-9701 improves active ghrelin levels in post-operation conditions.

Notably, the data in the paper reveals some information indicating DA-9701 as a prokinetic medication in promoting bowel peristalsis. The argument can be made for such study since it lacks vehicle control for DA-9701 that may increase a difficulty for data interpretation even difference existed in. We appreciate the authors' work and believe the DA-9701 research will be followed up in more detail in terms of mechanisms such as ghrelin levels and ghrelin receptor changes under DA-9701. Although data analyses is somewhat not comparable, it is informative and encouraging to clinicians.

Supplementary Material

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm17011.

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