

Peer Review File

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Reviewer A

The authors retrospectively analyse data from 46 neonates who underwent surgery for intestinal obstruction at their single-centre, over a 4-5 year period, with a focus on ostomy in continuity (OIC) procedures as the comparator.

Overall this is an important and interesting topic however the below must be addressed in regard to this manuscript.

1. In the abstract the authors have stated 'conclusions' twice, instead of 'results' and 'conclusions'. The abstract results would benefit from including statistics. The abstract sounds somewhat contradictory: results states that the OIC group had fewer post-operative complications, but the conclusion states that OIC is associated with common complications. Is there a statistics to justify this comment?

Reply : Thank you for the valuable suggestion, which is highly appreciated. We have revised the repeated 'conclusion' in the abstract to "result" and "conclusion" already. And the results of abstract have included the statistics as suggested. In addition, OIC, as a surgical procedure, still carries its own set of complications, albeit relatively fewer in comparison. The comparison between the two groups is statistically significant. The relevant data is shown as follow:

Parameter	OIC group (n, %)	Control group (n, %)	χ^2	P
Complications	4 (20.00%)	16 (57.14%)	5.556	0.018
High ostomy output	2 (10.00%)			
Diarrhea	1 (5.00%)	13 (46.43%)		
Anastomotic obstruction	1 (5.00%)			
Adhesive intestinal obstruction	1 (5.00%)	2 (7.14%)		
Stoma prolapse		1 (3.57%)		
Infection and stoma retraction		1 (3.57%)		

However, we strongly agree with your opinion, the relevant statement has been deleted in the revised manuscript as suggested.

Changes in the text:

Results: There were 18 patients underwent OIC, and 28 patients underwent double-barrel or single-barrel enterostomies. There were no statistically significant differences between patients in the two groups in terms of general information, duration of the ostomy surgery, bleeding volume, length of post-ostomy hospital stay, and time to first defecation after surgery ($P>0.05$). Compared to the control group, neonates in the OIC group had a shorter duration of parenteral

nutrition ($P=0.019$), a shorter interval between stoma creation and closure surgeries ($P=0.021$), a shorter duration of stoma closure surgery ($P<0.001$), and fewer postoperative complications ($P<0.001$). The weight-for-age Z-score before the stoma closure surgery was better in the OIC group than the control group ($P=0.010$).

Conclusion: In this study, we found that OIC, as a treatment for neonatal intestinal obstruction, was effective in maintaining intestinal continuity, improving the nutritional status of neonates, and shortening the interval between the stoma creation and closure surgeries. (page 2-3, line 36-49)

2. I'm confused how the authors managed to get 46 parents to sign a specific consent form for this study (lines 57-58), given that this is a retrospective analysis of clinical data from procedures between 2019-2024. From what I can see of the ethics reference, it infers 2021 approval.

Reply : Thank you for the professional comments, which is highly appreciated. We completely comprehend your apprehensions and uncertainties about this matter. Concerning the obtaining of informed consent from parents, in actuality, upon the hospitalization of the pediatric patients, we had already informed the parents that the pertinent information could potentially be utilized in future clinical research endeavors, ensuring concurrently the confidentiality of the minors' personal identifiers (e.g., names).

3. Regarding Methodology, the authors should present their search strategy (how did they identify these patients – e.g. through surgical database/ admission lists/ theatre lists etc.). They should also clearly state the total identified patients from this strategy, before stating where the exclusions occurred. How many patients were excluded because a second procedure occurred at a different hospital? Does this impact reporting of complications e.g. anastomotic leaks with OIC. Did any patients at the centre undergo primary anastomosis – if so, how many were thus excluded because of this? Authors also state the 'same group' of surgeons operated on all patients. This needs quantified/ expanded – is this the same two or three surgeons who operate on all cases, or is this a large department/group of 10 surgeons. It is also important to recognise that certain surgeons have preferences for post-operative management; is effect related to seniority/expertise of specific surgeons i.e. are more experienced or specific surgeons more likely to use the OIC procedure?

Reply : Thank you for taking time to review our article, which is highly appreciated. Actually, we utilized the hospital's electronic medical record system to gather pertinent cases employing search criteria inclusive of “neonatal necrotizing enterocolitis,” “meconium ileus,” “intestinal malrotation,” and “intestinal stoma procedures”. The relevant content has been added into the article as suggested. And totally 51 patients were identified from this strategy. As mentioned in the manuscript (page 7-8, line 171-179), 1 case in the OIC surgery group developed an anastomotic leak, leading to subsequent treatment at an external hospital, and was specifically noted in the text due to the particularity of the treatment process. In the control group, several patients, due to travel distance concerns, underwent stoma closure surgery at an external facility. These unique cases were confirmed via telephone correspondence. Additionally, in procedures such as NEC, instances of primary anastomosis were observed; however, as this manuscript centers on the analysis of pediatric patients who have undergone stoma surgery, these cases did

not fall within the scope of this statistical review. We have also included a flowchart to assist readers in better understanding our research process.

On the other hand, the surgical procedures in this cohort were carried out by four pediatric surgeons, all of whom possessed equivalent qualifications. Their experience and technical proficiency were closely matched. Comprehensive discussions and analyses of the pediatric patients' conditions in the perioperative period were conducted to ensure that the surgical strategies and quality were standardized and consistent. The relevant content has been added into the methods as required.

Changes in the text:

We collected the relevant cases through the hospital's electronic medical record system. (page 5, line 103-104)

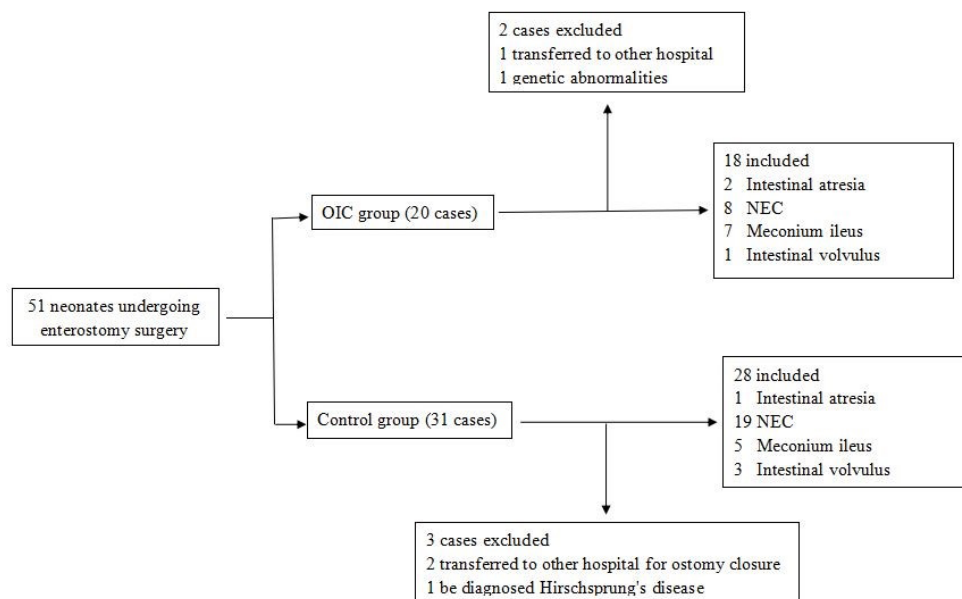
The surgical procedures in this cohort were carried out by four pediatric surgeons, all of whom possessed equivalent qualifications. Their experience and technical proficiency were closely matched. Comprehensive discussions and analyses of the pediatric patients' conditions in the perioperative period were conducted to ensure that the surgical strategies and quality were standardized and consistent. (page 4-5, line 115-119)

There were totally 51 patients identified from our strategy. Twenty neonates underwent OIC (Santulli/Bishop-Koop enterostomy). Among the 20 in the OIC group, one neonate was transferred to another hospital at the request of the family after reoperation due to an anastomotic leak, and another was taken home by the family after the neonate was diagnosed with abnormal genetic issues. Stoma closure surgery was completed in a total of 18 patients in this group.

In the control group, 31 infants underwent enterostomies. Among them, two infants had subsequent stoma closure surgery completed at another hospital, and one child was diagnosed with Hirschsprung's disease after surgery and excluded after undergoing radical surgery for Hirschsprung's disease. A total of 28 children underwent stoma closure surgery as scheduled, comprising seven neonates who underwent single-barrel stoma surgery and 21 who underwent double-barrel stoma surgery. Therefore, the study sample consisted of 46 neonates and the flowchart in Figure 1 showed our research process. (page 7-8, line 170-183)

Figure legends

Fig.1: The flow chart of patient inclusion in this study (page 16, line 375)



4. Authors describe the ‘choice of surgical approach’ which raises some questions. a) Is this all based on local protocol or agreement or just opinion of the authors (i.e. how can we qualify this was the decision making criteria for each case?); b) It is unclear how the surgeon would objectively quantify ‘risk of anastomotic leak’ in line 84 - maybe expand on this; c) The authors also state that the control groups were perhaps more unwell (or more likely to run into complications), compared with the OIC group: double-barrel ostomy was created for patients with severe intra-abdominal infections and single-barrel ostomy was created for patients ‘whose overall health condition was poor and unsuitable for prolonged surgery’. Therefore, it is surely no surprise that the OIC group will do better, as they are the 'better' surgical candidate? Reply : Thank you for your valuable feedback on our study. In response to the questions you raised, we provide the following additional explanations:

The choice of our surgical approach is based on a comprehensive set of considerations, including but not limited to, surgical guidelines and expert consensus for the relevant diseases. We determine the most appropriate surgical method based on the specific conditions of the pediatric patients, such as the presence of hypoproteinemia, severe infection, thrombocytopenia, and the length of the remaining healthy small intestine. We acknowledge that the decision-making process was not fully elucidated in the original manuscript and have included more detailed decision criteria and rationale in the revised draft to enhance transparency and reproducibility.

Regarding the quantification of the risk of anastomotic leak, we assess it based on a variety of clinical indicators, including blood supply to the intestine, tissue quality, intestinal preparation, and the overall health status of the pediatric patients.

Additionally, you correctly pointed out that the control group may have been at a higher risk of complications compared to the OIC group at baseline. We did indeed take note of this. When

selecting the control group, our intention was to provide an appropriate treatment plan for patients with severe intra-abdominal infections or those in poor overall health who were not suitable candidates for prolonged surgery. We agree that this might make the OIC group relatively "better" surgical candidates. We have further analyzed the potential impact of this baseline imbalance on the results in the discussion section under limitations and are considering the use of appropriate statistical methods to adjust for this difference in subsequent studies to ensure the accuracy and fairness of the research findings.

We appreciate the issues you have pointed out, which will help us improve the quality of the paper. We promise to elaborate on the above points in detail in the revised manuscript and to give full consideration to the opinions of the reviewers. Thank you again for your valuable comments.

Changes in the text:

In addition, while the primary aim of this study was to offer suitable therapeutic strategies for patients presenting with severe intra-abdominal infections or compromised overall health, making them poor candidates for extended surgical procedures, and despite the fact that the selection of the control group took into account the overall health and surgical risks of the pediatric patients, the control group may still have been at a higher baseline risk for complications compared to the OIC group. We will employ appropriate statistical methodologies in future research to adjust for this disparity, thereby ensuring the precision and impartiality of the study outcomes. (page 12, line 285-293)

5. Regarding the statistics - a minor request but please properly reference the SPSS software (SPSS Statistics + version + IBM). In line 116 the authors state they represented numerical data using percentages – please could the authors confirm that exact values (and not percentages) were used for chi-square and Fisher’s exact tests. It’s also unlikely that all continuous data were truly following a normal distribution given the very small sample size; perhaps a non-parametric test would be best? Data would benefit from multivariate analysis e.g. to adjust for confounding variables, although the sample size may be too small for this.

Reply : Thank you for the professional suggestion, which help improve the accuracy of the manuscript. We have revised the relevant content in the section of statistics as suggested.

Changes in the text:

Data were analyzed using the IBM SPSS Statistics 23. Chi-square tests were used for counting data, and Fisher exact tests were used when the expected count of a cell was less than 5. (page 7, line 162-164)

6. Regarding Results, including numerical values and statistics in the text would be helpful. There are no statistics presented for the data relating to complications i.e. between lines 149 and 153. This must be included, especially as complications are mentioned as a significant outcome throughout this manuscript. It is difficult to comment on complication rates when data are incomplete (in the discussion there is comment that a patient had an anastomotic leak at another centre but their data were excluded due to this; it’s impossible to contextualise this.

Reply : Thank you for the valuable suggestion and point out the shortcoming in the text. The relevant date and information have been added into the article as suggested. It is important to specifically note that one case in the OIC group developed an anastomotic leak, prompting the

family to pursue treatment at an external facility. As a result, we were unable to continue the follow-up on the subsequent treatment timeline and the condition during stoma closure surgery for this particular pediatric patient. In contrast, the control group, due to the distinct surgical technique employed and the absence of an anastomosis, did not encounter this complication. In the interest of providing an objective critique of the merits and demerits of the surgical approaches, this case, which stands as the sole instance, is highlighted individually for the readers' consideration in the discussion.

Changes in the text:

There was no statistically significant difference between the groups with respect to the time of performing the first ostomy, intraoperative bleeding volume, length of hospital stay after stoma creation surgery, or time to the first bowel movement. This finding can be attributed to our standard protocol, which mandates a minimum interval of 12 weeks between the stoma creation and closure surgeries, alongside a minimum body weight of 5 kg.^[14,15] Neonates in the OIC group had a significantly shorter duration of parenteral nutrition compared to the control group ($P=0.019$). (Table 2)

The two groups exhibited no statistically significant difference in terms of weight at stoma closure surgery or days of hospital stay after stoma closure surgery (Table 3). However, in comparison to the control group, neonates in the OIC group had a shorter interval between the stoma creation and closure surgeries ($P=0.021$), a shorter duration of surgery for stoma closure ($P<0.001$), less bleeding during stoma closure surgery ($P<0.001$). This disparity was most likely because neonates in the OIC group required only stoma closure without the need for more complex intra-abdominal procedures. And the OIC group showed better weight-for-age Z-scores than the control group.($P=0.010$) (Figure 2). We also noted that there was a decrease in the postoperative Z-score in the control group compared to pre-surgery Z-score.

An analysis of ostomy-related complications revealed that in the OIC group, a total of 4 infants (20.00%) experienced stoma-related complications. 2 patients (10.00%) developed high ostomy output (greater than 20ml/kg/d) after surgery. Both cases involved neonates who underwent the Santulli procedure, with the lengths of the proximal small bowel being 70 centimeters and 50 centimeters, respectively, against a total small bowel length of 95 centimeters and 105 centimeters. After ruling out infectious etiologies for diarrhea, the neonates were initially nourished with breast milk. Upon the onset of diarrheal symptoms, their diet was transitioned to a hydrolyzed formula with reduced osmolarity, yet the symptoms of diarrhea persisted despite these interventions. The condition of one of them improved after antidiarrheal treatment and stoma blockage. In the case of the other patient, an exploratory laparotomy was performed 8 weeks after the initial stoma creation surgery due to recurrent diarrhea and minimal anal defecation, subsequent to adequate parenteral nutrition and intestinal preparation. 1 neonate (5.00%) developed both diarrhea and anastomotic obstruction. The original stoma and anastomosis site were removed intraoperatively, and a direct anastomosis of the proximal and distal intestine segments was performed. One patient (5.00%) developed postoperative adhesive intestinal obstruction, which improved after conservative treatment was initiated.

In contrast, in the control group, 16 neonates (57.14%) had stoma-related complications, 13 neonates (46.43%) developed diarrhea, and this was significantly higher than that in the OIC group. Among them 1 (3.57%) developed stoma prolapse. One infant (3.57%) was treated for surgical site infection and a stoma retraction, while 2 infants developed adhesive intestinal

obstruction (7.14%). (Table 4) (page 8-10, line 187-227)

Table 4: Comparison of ostomy-related complications between the two groups

<u>Parameter</u>	<u>OIC group</u> <u>(n, %)</u>	<u>Control group</u> <u>(n, %)</u>	<u>χ^2</u>	<u>P</u>
<u>Complications</u>	<u>4 (20.00%)</u>	<u>16 (57.14%)</u>	<u>5.556</u>	<u>0.018</u>
<u>High ostomy output</u>	<u>2 (10.00%)</u>			
<u>Diarrhea</u>	<u>1 (5.00%)</u>	<u>13 (46.43%)</u>		
<u>Anastomotic obstruction</u>	<u>1 (5.00%)</u>			
<u>Adhesive intestinal</u> <u>obstruction</u>	<u>1 (5.00%)</u>	<u>2 (7.14%)</u>		
<u>Stoma prolapse</u>		<u>1 (3.57%)</u>		
<u>Infection and stoma</u> <u>retraction</u>		<u>1 (3.57%)</u>		

7. The Discussion is too long. The first few paragraphs would be better placed in the introduction (while very informative, they are too long for a concise manuscript). The next few paragraphs just state the results again and are superfluous. Sentences throughout the discussion need rephrased – you cannot definitely make conclusions without evidence (you can however say ‘most likely because of’) e.g. lines 203-205. Data must always include units of measurement e.g. lines 199, 201, 203, 221. Lines 224-227 are not supported by any data and should be removed – you did not directly measure nutrient absorption and weight is not a reliable surrogate for this.

Reply : Thank you for the kind remind, which is highly appreciated. The first few paragraphs have been removed to the introduction and been appropriately streamlined as suggested. The portion of the discussion that previously restated data from the results section has been excised and we also deleted the content about nutrient absorption as suggested.

Changes in the text:

For neonates, the optimal treatment strategy for the intestine retained after diseased segment resection is primary anastomosis of the remaining intestine. This maintains intestinal continuity, preserves the function of the distal intestinal segment, and avoids a second surgery. Primary anastomosis is preferred in terms of reducing nursing difficulty, shortening the hospital stay, and reducing hospital costs.^[6] However, in cases where the ratio of the remaining proximal and distal intestine segment diameter is greater than 4:1,^[7] or if there is severe intra-abdominal infection, direct anastomosis may lead to anastomotic leak, and the distal intestine segment may develop stenosis after treatment of NEC. In such cases, a temporary enterostomy is necessary. Enterostomy can be classified into single-barrel ostomy, double-barrel ostomy, and ostomy in continuity (OIC) (Bishop-Koop or Santulli), based on the surgical technique used.

Double-barrel or single-barrel stoma surgery has been favored in the past due to its simplicity and ease of implementation. However, intractable diarrhea frequently occurs after enterostomy among patients with a short proximal small intestine segment. This results in a significant loss of digestive juices, leading to fluid imbalance and electrolyte disorders. In such conditions, long-term total parenteral nutrition (TPN) treatment is often required, worsening the risk of sepsis, cholestasis, liver dysfunction, and venous catheter-related complications.^[8,9]

The OIC procedure comprises two primary techniques: the Santulli enterostomy and the Bishop-Koop enterostomy.^[10] Santulli's enterostomy was initially used to treat congenital intestinal atresia.^[11] In the early stages of its application, this procedure served to divert intestinal contents, relieve pressure on the anastomosis, and prevent anastomotic leaks. Once the edema at the anastomosis resolved, intestinal fluid could pass through the anastomosis into the distal intestine.^[12] The Bishop-Koop stoma was first used in 1955 for the treatment of meconium ileus.^[13] By gradually emptying the thick and dry meconium from the distal intestine segment, this technique facilitates the passage of contents from the proximal intestine segment into the distal intestine segment. This process not only improves nutrient absorption but also promotes dilation of the distal intestine segment. (page 3-4, line 64-93)

Discussion

Neonatal intestinal obstruction is a life-threatening condition, most of which requires emergency treatment. Because of the time limitation or the physical condition of the child, enterostomy is an important option for which can relieve the obstruction quickly. Different from adults, enterostomy in children is mostly temporary and has many complications. Diarrhea is related to the length of the remaining normal bowel. The incidence of postoperative stoma retraction and skin infection in our center is significantly lower than that in international reports, which may be related to the surgical skills of the surgeon, the choice of incision and postoperative nursing measure^[16,17].

Our study involved the use of OIC (Santulli enterostomy and Bishop-Koop enterostomy) for the treatment of neonatal intestinal obstruction and an evaluation of risks of OIC surgery. The duration of the initial surgery was slightly longer in the OIC group in comparison with the control group. This was most likely because of the more intricate surgical procedures adopted for neonates in the OIC group.^[18] When compared with the control group, although the OIC cohort did not exhibit superior operative time, due to the circumvention of disuse atrophy in the distal bowel segment associated with the stoma, a marked decrease in the potential for postoperative diarrhea, a reduction in the interstitial period prior to stoma closure, and the ease of care management, there is a pronounced preference for the OIC surgical approach. This preference has been corroborated through our routine communications with the caregivers of pediatric patients.

Preoperative intestinal preparation is essential before stoma closure surgery. This includes procedures such as instilling intestinal contents into the distal intestine segment in the case of patients undergoing double-barrel stoma surgery and performing anus-accessed enemas for patients prior to single-barrel stoma surgery. This has rarely been reported in the previous literature. Consequently, the interval between the stoma creation and closure surgeries in neonates of the OIC group was shorter in comparison with the control group. We did not find any significant difference between the two groups in the length of hospital stay after stoma closure surgery. This finding is inconsistent with previous reports.^[18] This may be due to the recovery of intestinal motility needs time.

There were no instances of cholestasis, liver function impairment, or central venous catheter-related complications. Our analysis revealed that neonates in the OIC group had a significantly lower incidence of postoperative complications in comparison with the control group, with the incidence of diarrhea being significantly lower in this group.

Nevertheless, it must be noted that in the OIC group, one infant with NEC had to undergo

Santulli enterostomy during surgery, followed by an anastomotic leak on the third postoperative day. These cases were excluded from the final analysis of the study as their subsequent treatment was not administered in our hospital. In contrast, there were no such severe complications in the control group due to the absence of intra-abdominal intestinal anastomosis. This underscores the possibility that, despite fewer postoperative complications, neonates in the OIC group could still develop intestinal anastomosis-related complications. Our conclusion was that infants experiencing an intra-abdominal infection due to intestinal perforation and infants with severe intestinal inflammation and edema were at risk of developing anastomotic leaks, and hence, continuous stoma surgery was not suitable in such cases. This is consistent with the views of Yue et al.^[18]

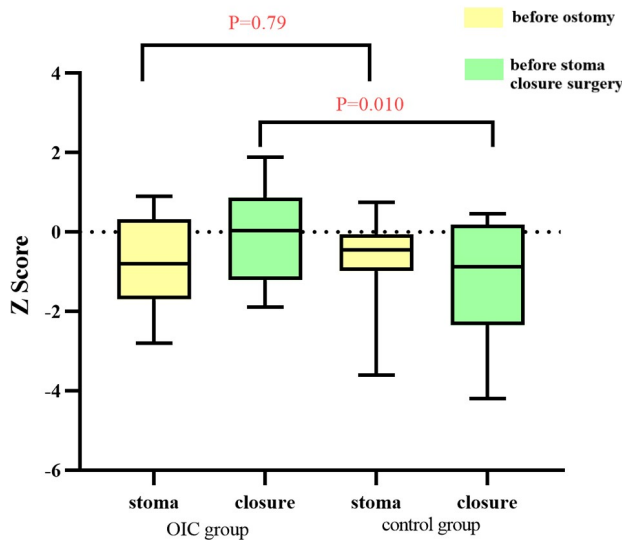
Due to the single-center design of the study, the generalizability of our findings is constrained by the small sample size. Furthermore, because of the limited number of patients who underwent Bishop-Koop enterostomy, a comparison of the advantages and disadvantages of the Santulli and Bishop-Koop enterostomies was not feasible in this study. Another limitation is that we only analyzed the nutritional status of the children through the weight Z-score and did not use the height-for-age Z-score, as some patients did not have their height measured before stoma closure. This aspect needs to be evaluated in future research. In addition, while the primary aim of this study was to offer suitable therapeutic strategies for patients presenting with severe intra-abdominal infections or compromised overall health, making them poor candidates for extended surgical procedures, and despite the fact that the selection of the control group took into account the overall health and surgical risks of the pediatric patients, the control group may still have been at a higher baseline risk for complications compared to the OIC group. We will employ appropriate statistical methodologies in future research to adjust for this disparity, thereby ensuring the precision and impartiality of the study outcomes. (page 10-11, line 230-293)

8. Figure 1 needs more descriptors – what does green and yellow boxes represent. This graph also questions whether it should be comparing the the CHANGE in z-scores, rather than raw z-scores?

Reply : Thank you for the valuable suggestion, which help improve the accuracy of the manuscript. The yellow boxes indicate the weight-for-age Z-scores of pediatric patients before stoma creation surgery; the green boxes signify the weight-for-age Z-scores prior to stoma closure. These modifications have been reflected in Figure 2. As for your second inquiry, we have indeed contemplated comparing the variations in Z-scores and determined that the original Z-scores are more vividly depicted using box plots, potentially correlating with factors such as the duration between the two surgical interventions.

Changes in the text:

Fig.2: Comparison of weight-for-age Z-scores before ostomy and before stoma closure surgery in the two groups



I do agree that these data are of interest to the paediatric surgical community however the above must be considered/addressed. If comparison is not appropriate, then authors could consider a descriptive case series.

Reply : Thank you for taking time to review our article. We are very pleased that you have offered numerous constructive suggestions that greatly benefit our study; this is of utmost importance for aiding us in elevating the caliber of our manuscript. We have revised the paper in accordance with your advice and hope it now satisfies your requirements. Additionally, we earnestly anticipate the opportunity to receive your esteemed feedback once more

Reviewer B

1> Title mentioned that this studied on intestinal obstruction, the NEC should be inflammatory disease rather be intestinal obstruction.

Reply : Thank you for your clarification. We concur with your viewpoint. Necrotizing enterocolitis (NEC) is indeed categorized as an inflammatory disorder, yet when its progression necessitates surgical intervention, the pediatric patients present with clinical manifestations of intestinal obstruction that intensify over time.

2> The aim of this study mentioned for investigate "the indications and precautions...". In my opinion, I think the indications in these cases should be your selection bias for considering whether the OIC or barrel ostomy should be used; the authors could not study out the indications from choices of ostomy.

Reply : Thank you for your advice. I apologize for not clearly stating the conclusion. The final part has been revised accordingly as well as the objective of abstract.

Changes in the text:

The study aims to evaluate the therapeutic efficacy of ostomy in continuity (OIC), providing a reference for surgeons to determine the appropriate surgical approach. (page 2, line 26-28)

In conclusion, our findings in this study indicated that OIC surgery was a feasible technique for addressing neonatal intestinal obstruction. As an ostomy method, OIC has a good performance in maintaining intestinal integrity, shortening parenteral nutrition time, and reducing the incidence of postoperative diarrhea. If short bowel syndrome is expected to occur during the operation, OIC is recommended. Of course, due to the existence of intraperitoneal anastomosis, the surgeon should pay attention to the occurrence of anastomotic fistula. When there are no factors affecting anastomotic healing, such as severe abdominal infection, hypoalbuminemia, and hemodynamic instability, OIC should be considered. (page 12-13, line 297-304)

3> In abstract, authors included 2 conclusion-sectors, and both sectors were unlikely to answer their study question.

Reply : Thank you for the valuable suggestion, which is highly appreciated. The relevant content have been revised as suggested.

Changes in the text:

Results: There were 18 patients underwent OIC, and 28 patients underwent double-barrel or single-barrel enterostomies. There were no statistically significant differences between patients in the two groups in terms of general information, duration of the ostomy surgery, bleeding volume, length of post-ostomy hospital stay, and time to first defecation after surgery ($P>0.05$). Compared to the control group, neonates in the OIC group had a shorter duration of parenteral nutrition ($P=0.019$), a shorter interval between stoma creation and closure surgeries ($P=0.021$), a shorter duration of stoma closure surgery ($P<0.001$), and fewer postoperative complications ($P<0.001$). The weight-for-age Z-score before the stoma closure surgery was better in the OIC group than the control group ($P=0.010$).

Conclusion: In this study, we found that OIC, as a treatment for neonatal intestinal obstruction, was effective in maintaining intestinal continuity, improving the nutritional status of neonates, and shortening the interval between the stoma creation and closure surgeries. (page 2-3, line 36-49)

4> The phrase of "corrected gestational age of less than 28 days" made the readers confused as it should be gestational age that was corrected; should it be at least more than 6 months in term of organogenesis has been completed in all these infants.

Reply : Thank you for the professional suggestion, which help improve the accuracy of the article. The phrase have been revised as suggested. In addition, in accordance with established clinical practice guidelines and expert consensus, stoma closure should be considered approximately at the 12-week mark for pediatric patients, provided their condition is amenable. This timing is advantageous for the restoration of intestinal continuity, which may enhance nutritional assimilation and ameliorate the caregiving demands placed on the parents.

Changes in the text:

...with gestational age (GA) that was corrected of less than 28 days (page 5, line 106)
gestational age that was corrected at the time of surgery (page 5, line 111)

Reviewer C

In this study, the authors report their experience in performing OIC in neonatal bowel injury/congenital malformation. The indications for each procedure are properly described. The comparative design of the study is very interesting and yields very informative results. However, the authors face one of the major obstacles of this type of study, which is comparability between both groups.

Reply : Thank you for your interest in our study and for the insightful comments you have provided. We fully concur that ensuring the comparability between groups in a comparative study is a critical consideration and has been a focal point in our study design.

In this research, we matched patients across groups based on key variables such as age, gender, disease severity and type of surgery. During the data analysis phase, we employed covariate adjustment and multivariate regression analysis to control for potential confounding factors. We have explicitly reported all inclusion and exclusion criteria, as well as the baseline characteristics of the patients in both groups within our study.

While these measures have been taken, we acknowledge that, due to the single-center nature of our study and the limited sample size, there may still be unidentified or uncontrolled confounding factors that could affect the comparability between the groups to some extent.

In response to your raised concern, we plan to enhance our future research by conducting multi-center studies to increase the sample size and reduce the bias associated with a single center. We will also consider a prospective study design to better control the research variables and the data collection process, and perform sensitivity analyses to assess the robustness of our results under different assumptions.

We appreciate your highlighting of this important issue and look forward to continuing to improve our research endeavors. We believe that with these measures, we can further enhance the quality and reliability of our research.

Thank you once again for your valuable time and suggestions.

General remarks

English language revisions are required.

Reply : Thank you for the valuable suggestion. We invited native English speakers to conduct a comprehensive language check on the revised manuscript.

Changes in the text: all manuscript

Title

I would suggest the following phrasing “a single-center comparative study” since it is a strength of the study.

Reply : Thank you for the valuable suggestion, which is highly appreciated. We have revised the title as suggested.

Changes in the text:

Treating neonatal intestinal obstruction with ostomy in continuity: A single-center comparative study (page 1, line 2)

Abstract

. Line 10: “based on condition differentiation” is a clumsy phrasing.

Reply : Thank you for the valuable suggestion. The phrase 'based on condition differentiation' has been removed. Meanwhile, this sentence has been rewritten.

Changes in the text: The study aims to evaluate the therapeutic efficacy of ostomy in continuity (OIC), providing a reference for surgeons to determine the appropriate surgical approach. (page 2, line 26-28)

. Line 11-14: This belongs to the results. The methods section should only describe the study design.

Reply : Thank you for pointing out the shortcoming existed in the article. We have revised it as suggested.

Changes in the text:

Methods: The study involved a retrospective analysis of the clinical data of 46 neonates with intestinal obstruction hospitalized between June 2019 and February 2024. The types of intestinal injuries included in the study comprised atresia, Necrotizing Enterocolitis (NEC), meconium ileus and volvulus. Based on their surgical procedures, patients were divided into the OIC group and the control group. General information, as well as perioperative and postoperative complications, were compared between the two groups.

Results: There were 18 patients underwent OIC, and 28 patients underwent double-barrel or single-barrel enterostomies. There were no statistically significant differences between patients in the two groups in terms of general information, duration of the ostomy surgery, bleeding volume, length of post-ostomy hospital stay, and time to first defecation after surgery ($P>0.05$). Compared to the control group, neonates in the OIC group had a shorter duration of parenteral nutrition ($P=0.019$), a shorter interval between stoma creation and closure surgeries ($P=0.021$), a shorter duration of stoma closure surgery ($P<0.001$), and fewer postoperative complications ($P<0.001$). The weight-for-age Z-score before the stoma closure surgery was better in the OIC group than the control group ($P=0.010$). (page 2, line 29-45)

. Line 17: The subheading should be “Discussion”.

Reply : Thank you for the comment. It is possible that the initial submission lacked the presentation of data and statistical analysis in the results section of the abstract, which may have led to a section that resembled a discussion rather than a presentation of findings. Following amendments, the current manuscript now includes quantitative data and, in keeping with the conventional format of a scientific abstract, the subheading 'Results' has been preserved in the revised draft. Once again, we appreciate your thoughtful feedback and welcome any additional comments or suggestions you may have.

Changes in the text:

Results: There were 18 patients underwent OIC, and 28 patients underwent double-barrel or single-barrel enterostomies. There were no statistically significant differences between patients in the two groups in terms of general information, duration of the ostomy surgery, bleeding volume, length of post-ostomy hospital stay, and time to first defecation after surgery ($P>0.05$). Compared to the control group, neonates in the OIC group had a shorter duration of parenteral nutrition ($P=0.019$), a shorter interval between stoma creation and closure surgeries ($P=0.021$), a shorter duration of stoma closure surgery ($P<0.001$), and fewer postoperative complications

($P < 0.001$). The weight-for-age Z-score before the stoma closure surgery was better in the OIC group than the control group ($P = 0.010$). (page 2, line 36-44)

. Lines 17-29: The results section should include p-values, at least when a significant difference has been found.

Reply : Thank you for the valuable suggestion. We have added the p-values into the results.

Changes in the text:

Results: There were 18 patients underwent OIC, and 28 patients underwent double-barrel or single-barrel enterostomies. There were no statistically significant differences between patients in the two groups in terms of general information, duration of the ostomy surgery, bleeding volume, length of post-ostomy hospital stay, and time to first defecation after surgery ($P > 0.05$). Compared to the control group, neonates in the OIC group had a shorter duration of parenteral nutrition ($P = 0.019$), a shorter interval between stoma creation and closure surgeries ($P = 0.021$), a shorter duration of stoma closure surgery ($P < 0.001$), and fewer postoperative complications ($P < 0.001$). The weight-for-age Z-score before the stoma closure surgery was better in the OIC group than the control group ($P = 0.010$). (page 2, line 36-44)

. The type of intestinal injury included in the study (atresia, NEC, meconium ileus, volvulus) should be shown in the abstract, either in the methods or the results section. Rephrasing of the some of the sentences from the abstract should allow the authors to include these data within the word limit.

Reply : Thank you for the professional advice. We strongly agree with your opinion. The relevant information have been added into the abstract.

Changes in the text:

The types of intestinal injuries included in the study comprised atresia, Necrotizing Enterocolitis (NEC), meconium ileus and volvulus. (page 2, line 31-32)

. Line 29: “necessitating” should be replaced by “requiring”.

Reply : Thank you for the comment, which is highly appreciated. We have deleted the sentence.

Changes in the text:

Conclusion: In this study, we found that OIC, as a treatment for neonatal intestinal obstruction, was effective in maintaining intestinal continuity, improving the nutritional status of neonates, and shortening the interval between the stoma creation and closure surgeries. (page 2-3, line 46-49)

. Keywords should probably include “Santulli” and “Bishop-Koop”.

Reply : Thank you for the kind remind. We have added the two keywords as suggested.

Changes in the text:

Keywords: intestinal lesions, neonatal intestinal obstruction, ostomy in continuity (OIC), ostomy surgery, Santulli, Bishop-Koop, treatment outcome. (page 3, line 51)

Introduction

. Line 38: “Malrotation” should be replaced by “malposition”.

Reply : Thank you for pointing out the mistake. We have revised it.

Changes in the text:

intestinal malposition (IM) (page 3, line 58)

. Line 39: “among other factors” should be removed. The authors could write “the most common causes” (line 36) instead.

Reply : Thank you for the comment, which is highly appreciated. We have deleted the statement as suggested.

Changes in the text:

Characterized by a rapid onset and high mortality, the most common causes include congenital intestinal atresia (CIA), necrotizing enterocolitis (NEC), meconium ileus (MI), Hirschsprung's disease (HD), intestinal malposition (IM), and anorectal malformation. (page 3, line 56)

. Lines 49-50: This sentence belongs to the methods section.

Reply : Thank you for valuable suggestion, which is highly appreciated.

Changes in the text:

Herein, the aim of this study was to assess the therapeutic effect of OIC and provide a reference for the choice of surgical approaches for intestinal obstruction. (page 4, line 94-95)

In this study, the clinical data of neonates with intestinal obstruction treated with OIC in our hospital between June 2019 and February 2024, were retrospectively analyzed. (page 5, line 99-100)

. Line 51: “Evaluate” should be replaced by “assessed”.

Reply : Thank you for the kind remind, which is highly appreciated.

Changes in the text:

Herein, the aim of this study was to assess the therapeutic effect of OIC and provide a reference for the choice of surgical approaches for intestinal obstruction. (page 4, line 94-95)

. Lines 51-52: This sentence is not clear enough. The aim should be rephrased.

Reply : Thank you for the suggestion. We have revised the sentence already.

Changes in the text:

Herein, the aim of this study was to assess the therapeutic effect of OIC and provide a reference for the choice of surgical approaches for intestinal obstruction. (page 4, line 94-95)

Methods

. Line 60: “Infants” should be removed since only neonates or included in this study.

Reply : Thank you for the kind remind. The word has been removed as suggested.

Changes in the text:

neonates with gestational age (GA) that was corrected of less than 28 days; (page 5, line 106)

. Line 62: “at our hospital”

Reply : Thank you for pointing out the mistake in the text. We have revised it already.

Changes in the text:

...who did not undergo initial or subsequent surgery at our hospital (page 5, line 114)

. Line 69: “The study sample consisted of 46 neonates” is a result.

Reply : Thank you for the comment. We have removed the sentence as suggested.

Changes in the text:

The surgical procedures in this cohort were carried out by four pediatric surgeons, all of whom possessed equivalent qualifications. Their experience and technical proficiency were closely matched. Comprehensive discussions and analyses of the pediatric patients' conditions in the perioperative period were conducted to ensure that the surgical strategies and quality were standardized and consistent. (page 5, line 115-119)

. Lines 70-81: These paragraphs belong to the results section.

Reply : Thank you for the valuable suggestion, which is highly appreciated. We have moved this part to the results section as suggested.

Changes in the text:

There were totally 51 patients identified from our strategy. Twenty neonates underwent OIC (Santulli/Bishop-Koop enterostomy). Among the 20 in the OIC group, one neonate was transferred to another hospital at the request of the family after reoperation due to an anastomotic leak, and another was taken home by the family after the neonate was diagnosed with abnormal genetic issues. Stoma closure surgery was completed in a total of 18 patients in this group.

In the control group, 31 infants underwent enterostomies. Among them, two infants had subsequent stoma closure surgery completed at another hospital, and one child was diagnosed with Hirschsprung's disease after surgery and excluded after undergoing radical surgery for Hirschsprung's disease. A total of 28 children underwent stoma closure surgery as scheduled, comprising seven neonates who underwent single-barrel stoma surgery and 21 who underwent double-barrel stoma surgery. Therefore, the study sample consisted of 46 neonates and the flowchart in Figure 1 showed our research process. (page 7-8, line 170-183)

. Line 83: “The surgical approach was based on intraoperative findings”.

Reply : Thank you for the valuable suggestion. We have revised the sentence as suggested.

Changes in the text:

The surgical approach was based on intraoperative findings (page 6, line 129)

. Line 89: I personally disagree with the author's indications for Santulli's procedure. In every case but meconium ileus, the goal of the stoma is decompression of the proximal bowel. Bishop-Koop's procedure has specifically been described for meconium ileus, for the purpose of distal bowel irrigation. One could argue that every neonate should have undergone a Santulli's procedure except for those with meconium ileus.

Reply : We extend our gratitude for your esteemed feedback. Your viewpoint is well-received and comprehended by our team. To be forthright, our approach to selecting a surgical technique

is grounded in the original elucidations by the progenitors of both procedures, complemented by a review of pertinent scholarly works. Our determination of the specific surgical modality is tailored to the unique clinical context of each pediatric case. It is evident that there exists a significant dearth of insightful prospective research on the comparative efficacy of these two surgical approaches on the international stage—a void we are resolved to explore within our forthcoming investigative endeavors. Once again, we appreciate your thoughtful feedback and welcome any additional comments or suggestions you may have.

. Line 93: I assume the authors mean “greater” instead of “less”.

Reply : Thank you for pointing out the mistake in our article. We feel so sorry that it was actually a clerical error. We have corrected it already.

Changes in the text:

...intestine segment was greater than 60 cm to minimize the risk of high-output stoma (page 6, line 138)

. Line 93: “Diarrhea” seems like a poor choice of words. The phrase “high-output stoma” seems more appropriate.

Reply : Thank you for the professional suggestion. We strongly agree with your opinion. And the relevant content has been revised.

Changes in the text:

...intestine segment was greater than 60 cm to minimize the risk of high-output stoma (page 6, line 138)

. The indication for stoma closure should be stated clearly in the methods section, e.g. when consistent bowel movement through the anus is observed and the child weighs at least 5kg for OIC.

Reply : Thank you for the reminder. The closure of the stoma is generally scheduled once the pediatric patient's weight has reached the threshold of 5 kilograms. The ability to defecate per anum is our intended outcome with the OIC procedure, and this functionality has been established shortly following the primary surgical intervention.

. The variable “time between stoma creation and closure” does not seem very appropriate to compare both groups. It is highly dependent on hospital logistics, potential anesthetic contraindications at the time of closure (e.g. viral infections) and prior intestinal preparation (as the authors do state in the discussion section).

Reply : Thank you for taking time to review our article. We concur with the rationale you've presented and recognize the merit in your viewpoint. The interoperative interval is certainly subject to a variety of influences; however, its principal determinant lies in the readiness of the pediatric patient's gastrointestinal preparation. These variations are, in essence, contingent upon the distinct surgical methodologies employed.

Results

. The authors should consider adding a flowchart in this section for clarity. I would advise that the flowchart contain the type of bowel injury in cases of OIC (who had which type of OIC procedure?).

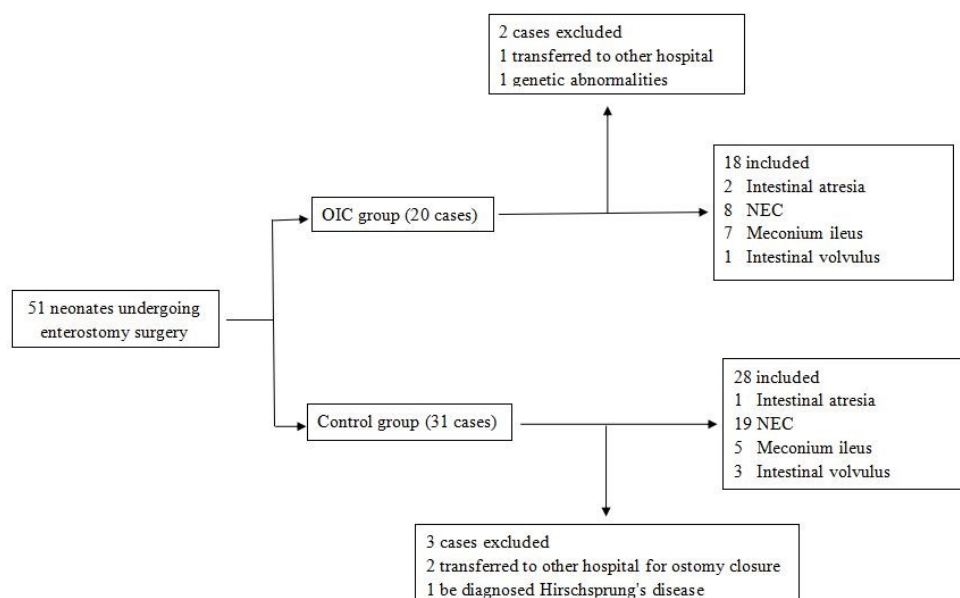
Reply : Thank you for the great advice, and we strongly agree with your opinion. The flowchart has been added into the article as suggested.

Changes in the text:

In the control group, 31 infants underwent enterostomies. Among them, two infants had subsequent stoma closure surgery completed at another hospital, and one child was diagnosed with Hirschsprung's disease after surgery and excluded after undergoing radical surgery for Hirschsprung's disease. A total of 28 children underwent stoma closure surgery as scheduled, comprising seven neonates who underwent single-barrel stoma surgery and 21 who underwent double-barrel stoma surgery. Therefore, the study sample consisted of 46 neonates and the flowchart in Figure 1 showed our research process. (page 8, line 176-183)

Figure legends

Fig.1: The flow chart of patient inclusion in this study (page 16, line 375)



. The subheadings within the results section can be removed.

Reply : Thank you for the comment. We have removed the subheadings within the results section as suggested.

Changes in the text: all manuscript

. Line 130: “defecation” is, to my best knowledge, rarely used in studies. The authors may want to consider rephrasing and more importantly differentiating bowel movement in the stoma and bowel movement through the anus.

Reply : Thank you for the valuable suggestion, which is highly appreciated. We have revised it as suggested.

Changes in the text:

or time to the first postoperative bowel movement. (page 8, line 189)

. Line 139-140: The authors should consider adding more details about these cases to try to explain the high output stoma: what was the level of the stoma? Did the children undergo Santulli's or Bishop-Koop's procedure? Did the children have enough small bowel? Were viruses excluded? How were they fed (orally? And if it was the case, were they given hyperosmolar milk? Total PN?).

.Reply : Thank you for the professional comment and the kind remind. Actually, both cases involved neonates who underwent the Santulli procedure, with the lengths of the proximal small bowel being 70 centimeters and 50 centimeters, respectively, against a total small bowel length of 95 centimeters and 105 centimeters. After ruling out infectious etiologies for diarrhea, the neonates were initially nourished with breast milk. Upon the onset of diarrheal symptoms, their diet was transitioned to a hydrolyzed formula with reduced osmolarity, yet the symptoms of diarrhea persisted despite these interventions. The relevant information have been added into the article.

Changes in the text:

Both cases involved neonates who underwent the Santulli procedure, with the lengths of the proximal small bowel being 70 centimeters and 50 centimeters, respectively, against a total small bowel length of 95 centimeters and 105 centimeters. After ruling out infectious etiologies for diarrhea, the neonates were initially nourished with breast milk. Upon the onset of diarrheal symptoms, their diet was transitioned to a hydrolyzed formula with reduced osmolarity, yet the symptoms of diarrhea persisted despite these interventions. (page 9, line 207-214)

Line 144: One of the benefits from OIC is that intestinal preparation is not needed. Was the intestinal preparation stimulation enemas to try to increase bowel movement through the anus?

Reply : Thank you for the valuable suggestion, which is highly appreciated. We apologize for any potential misuse of terms. The term "intestinal preparation" here specifically denotes the radiographic examination conducted prior to surgery. We utilize distal bowel contrast radiography to evaluate the configuration of the bowel and to identify any presence of bowel stenosis, thereby facilitating surgical planning. We have revised the statement already.

Changes in the text:

...subsequent to adequate parenteral nutrition and intestinal imaging studies (page 9, line 218)

. The authors never mention how the children were followed-up.

Reply : Thank you for the professional comments. In fact, we conducted follow-up on all pediatric subjects enrolled in the study, irrespective of whether it was prior to or following stoma closure. This follow-up was facilitated through a combination of telephonic communication, virtual consultations, and traditional outpatient clinic visits, with the aim of evaluating the subjects' growth, developmental progress, and defecation status. We have added the relevant information into the article.

Changes in the text:

We conducted follow-up with all the pediatric patients enrolled in our study via a multimodal approach, including telephone, online platforms, and traditional face-to-face outpatient clinic

visits, to evaluate their growth, development, and defecation patterns. (page 6, line 124-127)

Discussion/Conclusion

. Line 158: Intestinal continuity, intestinal segment

Reply : Thank you for the kind remind, which is highly appreciated. We have revised it as suggested.

Changes in the text:

This maintains intestinal continuity, preserves the function of the distal intestinal segment...
(page 3, line 66)

. Lines 194-195: There is no statistical difference here. And I would actually use that as an argument for OIC. Many people think that the procedure is much longer than “regular” stoma and therefore prefer to do the latter.

Reply : Thank you for the professional suggestion, which is highly appreciated. Your point is well taken. Indeed, when compared with the control group, the OIC cohort did not exhibit superior operative time. However, due to the circumvention of disuse atrophy in the distal bowel segment associated with the stoma, a marked decrease in the potential for postoperative diarrhea, a reduction in the interstitial period prior to stoma closure, and the ease of care management, there is a pronounced preference for the OIC surgical approach. This preference has been corroborated through our routine communications with the caregivers of pediatric patients. We have added the explanation into the discussion.

Changes in the text:

when compared with the control group, although the OIC cohort did not exhibit superior operative time, due to the circumvention of disuse atrophy in the distal bowel segment associated with the stoma, a marked decrease in the potential for postoperative diarrhea, a reduction in the interstitial period prior to stoma closure, and the ease of care management, there is a pronounced preference for the OIC surgical approach. This preference has been corroborated through our routine communications with the caregivers of pediatric patients.
(page 10-11, line 243-250)

. Lines 213-214: This could be explained by a lack of power in the study.

Reply : Thank you for your insightful comment regarding the potential lack of statistical power in our study. We acknowledge that the sample size may have limited our ability to detect smaller but clinically relevant effects.

We agree that this could have influenced the robustness of our findings. And we mentioned it in the limitation. (page 12, line 278-279)

Moving forward, we are committed to addressing this limitation by planning studies with adequate power. This includes strategies such as increasing the recruitment efforts, leveraging multicenter collaborations, and employing more efficient study designs. We believe these measures will enhance the reliability and generalizability of our research outcomes

Changes in the text:

Due to the single-center design of the study, the generalizability of our findings is constrained by the small sample size. (page 12, line 278-279)

. Line 223: “compared to pre-surgery Z-score” may be a better phrasing.

Reply : Thank you for the professional advice. We have revised it as suggested.

Changes in the text:

We also noted that there was a decrease in the postoperative Z-score in the control group compared to pre-surgery Z-score (page 9, line 203-204)

. Lines 238-250: This is a very important message. OIC still bears the risk of a bowel anastomosis and should not be performed at initial surgery for NEC because the goal of that procedure is solely to shunt the fecal flow and relieve the bowel.

Reply : Thank you for the valuable suggestion. We have made explanation in the discussion. We fully acknowledge the concerns you've raised here. We also recognize that there is a risk of anastomotic leakage in NEC patients undergoing OIC surgery. We only opt for this surgical approach when, after assessment, the disease is found to be relatively localized, the intestine at the anastomotic site is free from inflammatory lesions, and there is a potential risk of postoperative diarrhea.

Changes in the text:

This may be due to the recovery of intestinal motility needs time. (page 11, line 259-260)

. Although there was no difference between both groups in terms of type of bowel injury, children who underwent OIC had, by definition, a less severe bowel and/or general disease than the ones in the “regular” stoma group (e.g no hemodynamic instability, no abdominal infection etc). This difference alone could explain the shorter duration of PN and the lower rate of high output stoma, as the bowel from the OIC children could have needed less time to recover than the other group. This should be highlighted in the discussion section as a limitation and the conclusions should be nuanced on the matter.

Reply : Thank you for the valuable suggestion, which help improve the quality of the manuscript. We have added the relevant content into the article.

Changes in the text:

As an ostomy method, OIC has a good performance in maintaining intestinal integrity, shortening parenteral nutrition time, and reducing the incidence of postoperative diarrhea. If short bowel syndrome is expected to occur during the operation, OIC is recommended. Of course, due to the existence of intraperitoneal anastomosis, the surgeon should pay attention to the occurrence of anastomotic fistula. When there are no factors affecting anastomotic healing, such as severe abdominal infection, hypoalbuminemia, and hemodynamic instability, OIC should be considered. (page 12-13, line 297-204)