

Accepted version

Licence: CC BY-NC-ND

Please cite as:

Gabriele LISI (2024) "Opera mia" Journal of Pediatric Surgery

Journal Pre-proof

A Structured training for Trans Anal Irrigation in Pediatric patients Improves Outcomes and Reduce Failures: Results of an Interventional Multicenter Prospective Study

A. Pini Prato, C. Perretti, M. Erculiani, G. Mottadelli, M. Taverna, F. Giordano, A.M. Caruso, P. Magro, R. Guanà, E. Carretto, C. D'Aleo, G. Lisi, G. Masnata, M. Cheli, L. Migliazza

PII: S0022-3468(24)00002-2

DOI: <https://doi.org/10.1016/j.jpedsurg.2023.12.024>

Reference: YJPSU 61397

To appear in: *Journal of Pediatric Surgery*

Received Date: 17 November 2023

Revised Date: 16 December 2023

Accepted Date: 25 December 2023

Please cite this article as: Pini Prato A, Perretti C, Erculiani M, Mottadelli G, Taverna M, Giordano F, Caruso A, Magro P, Guanà R, Carretto E, D'Aleo C, Lisi G, Masnata G, Cheli M, Migliazza L, A Structured training for Trans Anal Irrigation in Pediatric patients Improves Outcomes and Reduce Failures: Results of an Interventional Multicenter Prospective Study, *Journal of Pediatric Surgery*, <https://doi.org/10.1016/j.jpedsurg.2023.12.024>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Elsevier Inc. All rights reserved.



A structured training for Trans Anal Irrigation in pediatric patients improves outcomes and reduce failures: Results of an interventional multicenter prospective study

Pini Prato A¹, Perretti C¹, Erculiani M¹, Mottadelli G¹, Taverna M², Giordano F², Caruso AM³, Magro P⁴, Guanà R⁴, Carretto E⁵, D'Aleo C⁶, Lisi G⁷, Masnata G⁸, Cheli M⁹, Migliazza L⁹

¹ Umberto Bosio Center for Digestive Diseases, The Children Hospital, AO SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

² Department of Surgery, Pediatric Urology Unit, Children's Hospital Meyer, IRCCS, University of Florence, Firenze, Italy

³ Pediatric Surgery, Azienda Ospedaliera Civico di Cristina Benfratelli, Palermo, Italy

⁴ Medium Intensity Surgery, OIRM Ospedale Infantile Regina Margherita AO Città della Salute e della Sienza, Torino, Italy

⁵ Department of Pediatric Surgery and Pediatric Minimally Invasive Surgery and New Technologies, San Bortolo Hospital, Vicenza

⁶ Spina Bifida Center, Azienda Sanitaria Provinciale, Caltanissetta, Italy

⁷ Pediatric Surgery at the Civil Hospital, Pescara, Italy

⁸ Pediatric Urodynamics, Azienda Ospedaliera G Brotzu, Cagliari, Italy

⁹ Pediatric Surgery Unit, ASST Papa Giovanni XXIII, Bergamo, Italy

ADDRESS FOR CORRESPONDENCE:

Alessio Pini Prato, MD

Director of Pediatric Surgery

Umberto Bosio Center for Digestive Diseases

The Children Hospital

AO SS Antonio e Biagio e Cesare Arrigo

Alessandria, Italy

Tel +390131207218

Mobile +393471327431

E-mail apini@ospedale.al.it

ABSTRACT

BACKGROUND – Continence issues due to organic causes including previous colorectal surgery or neurological issues might benefit from Tran Anal Irrigation (TAI) that proved to be highly effective but with a number of limitations including a relatively high discontinuation rates. Our study was aimed at evaluating the efficacy of an advanced protocol tailored to each patient to prevent dropout and increase satisfaction, independence, and quality of life.

MATERIALS AND METHODS – This was a prospective, interventional, multicenter, nonrandomized study involving children aged 4 to 18 years with bowel dysfunction unresponsive to conventional treatments who required TAI. TAI was performed in accordance to the best standards of care with a total irrigation volume that was determined based on low emission X-Ray barium enemas performed at the very beginning of the study. All patients underwent training and assessments of continence, patients' perspectives and quality of life were performed at different timepoints from enrollment (T0) up to 6 months since TAI was introduced (T3).

RESULTS – A total of 78 patients were enrolled. Male to female ratio was 1.4:1. Mean age at enrollment was 106.1 ± 42.8 months. Discontinuation was reported by 3 patients (3.8%). Continence, satisfaction and a number of other outcome measures increased from baseline (T0) to the last visit (T3). In particular, mean Rintala total score increased linearly from 7.8 to 14.8 during the study period (T0 to T3 timepoints). On a multivariate analysis, the only parameter that proved to be inversely associated with continence as well as with other outcome measures was the use of laxatives at enrollment and during the study.

CONCLUSIONS - This study has demonstrated the high efficacy of this innovative patient-tailored TAI protocol across all assessed scores. Of note, given the negative impact of laxatives, our findings suggest limiting their use in this patient population to further increase the efficacy of the procedure.

KEYWORDS: Bowel dysfunction; Transanal irrigation; Peristeen; Anorectal malformation; Hirschsprung; Continence

BACKGROUND

Bowel dysfunctions (BD) such as constipation and fecal incontinence (FI) occur in up to 30% of children and adolescents, and may be due to functional or organic disorders (1). Organic causes can be further divided into neurogenic disorders, such as central nervous system (CNS) disorders or anatomical malformations affecting the spinal cord (e.g., spina bifida – SB), and post-operative issues occurring in patients operated on for Hirschsprung's disease (HSCR) or anorectal malformations (ARM) without CNS and spinal cord involvement (1,2). Regardless of the cause, symptoms of BD are associated with stressful events for both patients and caregivers, and both adolescents and children report poor health-related quality of life (QoL) and social problems, including difficulty socializing with peers (1–3).

Clinical management of BD in children consists of a hierarchical sequence of therapies that begins with conservative approaches and progresses over time with treatments of increasing invasiveness (3,4). Transanal irrigation (TAI) is a minimally invasive treatment widely used in children and adults when they do not respond to conservative treatment options (5,6). TAI involves large-volume water irrigation of the rectum and colon via the anus to facilitate a period of fecal continence and/or to relieve constipation; it is usually well tolerated and has a low incidence of major side effects (6–8). Most of published pediatric studies on TAI show high rates of improvement in bowel function and health-related quality of life (HRQoL), for both organic and functional conditions (3,9–13). However, the impact of treatment on the quality of life of caregivers and family members of patients who require assistance, has not been fully investigated (16).

Despite the positive results of recent studies of TAI in pediatric patients (6) and the publication of general best practices (5,6,16), there are few prospective studies with robust conclusions (16), and most clinical evidence comes from retrospective studies with varying lengths of follow-up (8,9,17,18). Moreover, the use of TAI in pediatric population is associated with high dropout rates reaching up to 30% (9,11,12,18,19), which seem to improve with individualized training by qualified personnel (20,21).

The aim of this study was to evaluate the efficacy of an advanced protocol tailored to each patient or condition, to prevent dropout, and to evaluate outcomes in terms of satisfaction, bowel management, independence, and quality of life in children and their caregivers.

MATERIALS AND METHODS

Inclusion criteria

This prospective, interventional, multicenter, nonrandomized study involved children aged 4 to 18 years with BD (including FI and constipation) unresponsive to conventional treatments and with a subsequent indication to TAI. Patients were divided into two groups according to their clinical condition.

Group A

Patients with BD due to organic causes, without CNS and spinal cord involvement:

- ARM
- HSCR
- Pediatric Intestinal Pseudo-Obstruction (PIPO)

Group B

Patients with BD due to organic neurological causes, involving either CNS or spinal cord:

- SB
- ARM with spinal cord involvement
- Other diseases with spinal cord involvement (tumors, trauma, etc.)

Exclusion criteria

Exclusion criteria were as follows:

- acute/chronic inflammatory bowel disease
- colorectal stenosis or other conditions requiring surgical treatment
- ischemic colitis
- anal/colorectal surgery within 3 months before the study
- TAI treatment within 6 months before the study

Ethical considerations

The study was approved by the Ethical Committees of all participating centers coordinated by the Umberto Bosio Center, The Children Hospital, AO SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy (Coordinating Center Approval Prot. No. 0013688). The study was designed

thanks to the collaboration of 9 Italian centers and was conducted in 5 of them. A complete list of the centers that contributed to the study is provided in the acknowledgments section.

Device used during the study

The Peristeen® device (now on the market as Peristeen® Plus), manufactured by Coloplast A/S (Humblebaek, Denmark), was used throughout the study.

Protocol

Study visits are summarized in Figure 1. Within eight weeks after recruitment (T-1), patients (together with their families) were trained in the use of the TAI device (T0) according to well-known practices (5). In particular, plain water was used for irrigation during TAI. During the T0 visit, patients underwent a psychological and instrumental assessment including a low-dosage barium enema with fluoroscopic assessment in order to determine the exact amount of fluid required for daily irrigation. One week later (T1), correct use of TAI and bowel function (Rintala and Visick scores) (27-29) were addressed. TAI was used daily during the first month of treatment, every other day afterwards unless differently indicated. We also assessed the presence of pain during defecation, bleeding during defecation, sensation of incomplete bowel emptying, feeling of not being able to empty, bowel emptying time, need for laxatives, and incidence of urinary tract infections. Patient perception of their clinical condition, social acceptance and satisfaction were assessed using dedicated questionnaires including Visick, VAS and Wong-Baker scales (29,30). Follow-up was conducted face-to-face and/or by telephone call at 8 weeks (T2) and 6 months (T3) after starting TAI.

Barium enema

Barium enema was performed under fluoroscopy with low dosage emission of X-rays with a conventional X-Ray fluoroscopic device. Dilute radiopaque contrast medium was instilled through a rectal tube (size according to patients' age) and a maximum of 5 fluoroscopic acquisitions were obtained to assess the total volume needed to irrigate the entire left colon. The volume was determined as the exact amount of diluted contrast needed to reach the splenic flexure of the colon.

Scoring and questionnaires

The following questionnaires for bowel function and patients' perspectives were used

- *Rintala* score to determine the severity of continence issues. Continence was defined as Poor (≤ 6), Fair (7-11), Good (12-17), Normal (≥ 18) (27,28)
- *Visick* score to determine patients' perspectives of outcome (29)

- *VAS* score or *Wong-Baker* scale to determine patients' perception of acceptance (30)

Statistical analysis

Patient's characteristics as well as their clinical evaluations were summarized using either count and percent or mean and Standard Deviation (SD) or Interquartile Range (IQR) for categorical and continuous variables. A sample size calculation was performed to determine the minimum number of patients to include. With a 95% confidence interval (CI) half-width of approximately 10% (margin of error) and a dropout rate of 10%, approximately 80 patients needed to be included to reach 72 completes. The Shapiro-Wilk test was used to test the normality assumption. Repeated measurements analysis of variance (RM-ANOVA) was done for all clinical variables with at least two measurements evaluated at each scheduled visit. Ordinal and binary variables were analyzed using either a mixed effects proportional odds (PO) model or the logistic regression model respectively, using patient's ID as the only random effect. Pairwise comparisons for each visit with respect to baseline were tested for significance using the type III fixed effects F-test. RM-ANOVA parameters estimates (β) were tabulated alongside Standard Errors (SE) for the continuous outcomes, odds-ratios (OR) were tabulated alongside 95% CI for the PO and the logistic regression analyses. Multivariate analyses were run by selecting only the statistically significant effects at the univariate analyses and excluding the collinear ones. All tests were two-tailed and considered significant at the 5% level. All analyses were done using SAS 9.4 (Cary, NC, USA)

RESULTS

Demographics and clinical features

A total of 78 patients participated in the study. Male to female ratio was 1.4:1. Mean age at enrollment was 106.1 ± 42.8 months. Mean height and weight were 129.1 ± 21.9 cm and 29.6 ± 14.0 kg respectively. All patients suffered from organic cause of BD, 34 (43.6%) of whom being neurological (group B). Seventeen (21.8%) patients were operated on for isolated ARM, whereas 12 (15.4%) for ARM with associated spinal cord issues. Fifteen patients (19.2%) suffered from HSCR. Eighteen (23.1%) had SB. The remaining 16 (20.5%) patients had heterogeneous clinical conditions, neurological in 4 cases and organic in 12. No cases of PIPO were eligible and enrolled. See Table 1 for details.

Training and procedure

All patients were "trained" in the use of Peristeen device through an explanation lasting an average of 79 ± 32.8 minutes. A total of 33 patients required assistance to use the device (42.9%), 26 patients to fill it (33.8%), 19 to pump out the water (24.7%), 18 to lubricate the catheter (23.4%), and 5 to insert the catheter (6.6%).

At TAI training, patients had a mean calculated enema volume of 329 mL (IQR:200,400), which was increased to 342 mL at T2 and 357 mL at T3 (mean change of +24 mL). The increase turned out to be significant at T3 ($p=0.01$). There were no factors significantly associated with the change in enema volume at T2 and T3, except for pre-treatment volume, which showed that the higher the volume at baseline (OR = 0.76, 95%CI: 0.61,0.93), the lower the odds ratio for an increase at T2 or T3 ($p = 0.009$).

Demographics comparing Groups

Overall, there were no significant differences between groups A and B except for mean height (135.5 vs 122.0 cm, $p = 0.009$), mean weight (32.8 vs 25.2 kg, $p = 0.006$) and frequency distribution (32.4% vs 12.2%, $p = 0.03$) of autonomous patients using the device for groups A and B respectively (Table 1).

Efficacy endpoints

Discontinuation

Overall TAI was maintained throughout the study by all patients but 3 who discontinued treatment and left the study (3.8%). In one case the discontinuation occurred without providing a reason and in 2 cases the patient refused to continue TAI due to abdominal pain and feelings of anxiety or tightness during irrigation.

Rintala score

Mean Rintala total score increased linearly from 7.8 at baseline to 14.8 at the last visit (Figure 2). Univariate analysis showed a significant difference for each time point (T1, T2, and T3) compared to the baseline T0 ($p < 0.001$). Even if the only statistically significant difference was observed with relation to T0, the improvement in the score increased with the whole duration of device use (Table 2). Other factors significantly associated with an improvement in the Rintala score in univariate analysis were higher enema volumes ($\beta = 0.47$ mL, $p = 0.01$), not being affected by SB ($\beta = -1.93$, $p = 0.01$), and not using laxatives ($\beta = -3.54$, $p < 0.001$). Rintala score significantly increased also with age ($\beta = 0.03$, $p < 0.001$), weight ($\beta = 0.07$, $p < 0.001$) and height ($\beta = 0.5$, $p < 0.001$) though the effect was quantitatively less relevant. On multivariate analysis, the only parameter that improved the score besides the duration of treatment was the use of laxatives that remained a significant inversely associated factor ($\beta = -1.65$, $p < 0.001$), consequently related with a worsening of the condition (Table 2).

Frequency distribution analysis of Rintala mean score revealed that the number of patients reporting Poor or Fair scores decreased significantly over time, from 76.9% at T0 to 14.7% at T3, with no cases of Poor score at T3; at the same time the number of patients with Good (12-17) or Normal (≥ 18) scores increased from 23.1% at T0 to 85.3% at T3 (Table 3).

Pain during defecation

The percentage of patients complaining of pain during emptying decreased from 24.4% at the first visit to 13.3% at the last visit, while the percentage of patients reporting no pain during bowel emptying increased from 71.8% to 86.7% (Figure 3A). Duration of treatment (T2 vs T0: OR = 4.15, $p = 0.009$, T3 vs T0: OR = 4.79, $p = 0.005$) and laxative use (OR = 0.29, $p = 0.02$) were the only two factors significantly associated with an improvement in univariate analysis, but these were not confirmed in multivariate analysis.

Bleeding during defecation

Bleeding during defecation was reported in only a few cases at baseline (6.4%) but continued to decrease after 6 months of TAI treatment (2.7%) (Figure 3B). There were no significant changes nor factors associated with it, compared to baseline.

Sensation of incomplete bowel emptying and failure/no sensation to empty

The sensation of incomplete bowel emptying and failure/no sensation to empty decreased over time in the study group, and the percentage of patients who did not report these sensations increased from 28.2% at T0 to 72.0% at T3 and from 35.8% at T0 to 61.2% at T3, respectively (Figure 3 C and D). The improvement was significant in both sensations analyzed (i.e., incomplete bowel emptying and failure to empty) for any time comparison with T0 ($p < 0.001$). In the univariate analysis several parameters (i.e., autonomy in using the device: OR = 0.32, $p = 0.001$; autonomy in filling the device: OR = 0.38, $p = 0.008$; laxative use: OR = 0.36, $p = 0.003$) were found to negatively affect the feeling of “incomplete bowel emptying”, but in multivariate analysis only the need for laxatives remained a significant parameter (OR = 2.53, $p = 0.01$), providing an improvement of the sensation to empty. The univariate analysis for the sensation “failure/no sensation to empty” reported an inverse association with the underlying condition of ARM with neurological involvement (OR = 0.06, $p = 0.002$) and the need for laxatives (OR = 0.27, $p = 0.007$), but again multivariate analysis confirmed the association only for the neurological ARM condition (OR = 0.29, $p = 0.04$).

Urinary tract infections

Urinary tract infections, which occurred in 23.1% of cases at T0, significantly decreased to 2.6%, 5.3% and 8.0% at T1, T2 and T3 respectively ($p < 0.001$).

Bowel emptying time

Bowel emptying time also improved with TAI use, with the number of patients reporting emptying times > 30 minutes decreasing from 31.3% (T0) to 14.7% (T3) with need for laxative use similarly decreasing from 62.8% (T0) to 32.0% (T3). Univariate analysis of bowel emptying time showed duration of treatment, age, weight and height as factors significantly associated with the proportion of patients requiring < 30 min for empty, however at the multivariable analysis only the duration of

treatment still retained its significance (T1: OR 5.05, 95%CI 1.67,15.2, $p = 0.004$; T2: OR 6.51, 95%CI 1.98, 21.4, $p = 0.002$; T3: OR 4.05, 95%CI 1.34,11.9, $p = 0.01$).

Satisfaction

We could observe an improvement in satisfaction reported by parents/caregivers. As shown in Table 4, the percentage of subjects reporting a grade I Visick score almost doubled between T1 and T3 (from 48.1% to 82.7%), whereas the percentage of patients reporting all other levels (II, III and IV) significantly decreased ($p < 0.001$). Univariate analyses showed that laxative use and increased TAI volume were parameters significantly associated with a change in Visick grade, confirmed in multivariate analysis, the former being a significant barrier to improvement (OR: 0.15; $p=0.008$) and the latter increasing satisfaction (OR: 2.18; $p=0.009$). Child height was univariate but not multivariate significant (Table 4).

Self confidence

The mean VAS score for *self-confidence* decreased significantly from a baseline of 2.6 to 1.7 at T1 ($p < 0.001$) to 1.4 ($p < 0.001$) at T2 to 1.3 at T3 ($p < 0.001$); the need for laxatives was significantly associated with a worse score in univariate analysis ($\beta = 1.02$, $p < 0.001$), but it was not confirmed in multivariate ($\beta = 0.31$, $p = 0.12$). On the other hand, the mean VAS score for the item *problems with friendship* decreased significantly from a baseline of 1.9 to 1.4, 1.2 and 1.0 at T1, T2 and T3 respectively ($p < 0.001$). Again, need for laxatives was significantly associated in univariate analysis ($\beta = 0.82$, $p < 0.001$), but no in multivariate. Also, higher enema volume was significantly associated with lower satisfaction in the univariate analysis ($\beta = -0.30$, $p = 0.03$) but not in the multivariate analysis ($\beta = 0.31$, $p = 0.11$). Training duration was associated with higher satisfaction ($\beta = 0.45$, $p = 0.02$), but not confirmed with multivariate analysis ($\beta = 0.35$; $p = 0.16$).

Group comparison

When we compared all the outcomes studied between group A and group B patients, no significant differences were found, confirming TAI benefits uniformly achieved in both study populations.

DISCUSSION AND CONCLUSIONS

TAI is considered an effective therapeutic intervention for the treatment of BD in all age groups, but there is limited scientific evidence from comprehensive prospective studies in children, especially to evaluate long-term effects. In addition, there is no uniform consensus on the ideal treatment in children, and the social impact on families is not yet fully understood (16, 22). The goal of irrigation is to flush the stools out of the left colon to allow a period free from accidents preventing leakage between irrigations. To date, few reports have been published on the efficacy of TAI in children with BD (22), and to the best of our knowledge, this is the first study to evaluate the effect of a patient-tailored TAI protocol in children with organic BD, with objective analysis of bowel function and child and caregiver satisfaction using validated scores.

The outcomes of our study went beyond the existing literature by underscoring the substantial benefits of a patient-tailored TAI protocol. In fact, although prior studies on childhood BD have reported favorable outcomes with TAI, they exhibited variable success rate, ranging from 28% to 93%, in the treatment of fecal incontinence and constipation (4,18,19,23-25). Other reports described a meaningful improvement of quality of life (9,11,26) though complete fecal continence and independence were described in around half of the patients addresses on this regard (1,4,18,24,25). The heterogeneity of the reported results could be related to the lack of standardized treatment as well as that of personalization for patients based on clinical features and diseases. Moreover, the absence of validated questionnaires specifically dedicated to pediatric BD and continence disorders (12,20) may also constitute a major limitation in the analysis of the effectiveness of TAI.

Therefore, the aim of the present study was to assess the efficacy of TAI in two major groups of pediatric patients (organic BD with and without neurological causes) using objective and reproducible parameters and validated questionnaires. As a matter of facts the two groups of patients did not significantly differ from a demographic point of view and did not exhibit statistically significant variations in outcomes, except for weight and height. This difference can be explained considering that patients with BD resulting from neurogenic disorders, such as SB, are generally enrolled at a younger age given the severity and non-reversibility of their neurogenic issues. Furthermore, the presence of SB was confirmed as a parameter that interfered with a number of outcome measures.

The improvements of the Rintala Score represents one of the most relevant aspects of TAI. This Score proved to be the most reliable scoring system to address continence in pediatric patients even those receiving TAI. Even so, there is the risk of underestimating the real improvement obtained with the procedure as the first two items in the scoring system are poorly assessed during transanal irrigation. This aspect must be considered when counseling patients on this regard.

During the study period we could observed an increase of the scores that are consistent to what observed in other studies at 6- to 14-month follow-up (4,11,17,22). In particular, Fair to Poor continence basically disappeared during treatment with only a minority of the patients (less than 15%) complaining major continence issues at the end of the study period, after 6 months of continuous TAI. Of note, the patients who experienced the worst results have been those with a regular use of laxatives and those who suffer from SB that thus proved to be independent risk factors of poor outcome. This is not unexpected if we considered the loosening effects of laxatives on stools and the difficult bowel management in case of diarrhea. Although with a lower level of significance, SB acts as a worsening factor due to the poorer perineal muscle floor leading to minimal to no continence potential.

We also observed that the higher the initial volume of TAI, the higher is the improvement of Rintala score as well as other addressed scores. Again, this might be correlated to the presence of a dilated rectum that benefits most from TAI given the emptying role of the procedure. For this reason, the personalized approach seems crucial in achieving patient satisfaction, as suggested by the design of this study. The use of barium enemas at the first visit allows the amount of fluid used for TAI to be optimized, thus ensuring effectiveness and patient satisfaction.

All other parameters and outcome measures including pain and bleeding during defecation and sensation of incomplete to no emptying dramatically improved during TAI. Improvement showed a direct relationship with overall treatment duration and an inverse relationship with laxative use. Again, we could confirm how a long-lasting and consistent use of TAI provides the best results and how regular laxative use may interfere with overall expected outcome.

Of note, laxative use was also significantly associated with worse Visick grades in both univariate and multivariate analyses, confirming how laxatives may negatively affect quality of life/satisfaction.

Previous literature reports failed in identifying these negative effects of laxatives on outcome, symptoms, perspectives, and satisfaction in patients using TAI, suggesting that further studies are needed to possibly confirm this relationship and develop tailored treatment or therapeutic adjustments.

This study has some limitations, including the lack of a control population. Nevertheless, our results clearly demonstrated that TAI is a successful treatment for children with organic BD who do not respond to conventional conservative treatments, regardless of the underlying cause of symptoms. The evident superiority of this therapeutic and rehabilitative approach over other alternatives made it unethical to propose an RCT on this topic. In the future we could address different available devices with an RCT to determine a superiority of one over the other, if present.

The possibility to even improve outcome by standardizing the approach and the methodology of TAI is confirmed by our enthusiastic results and by the extremely low dropout rate in our study that proved to be meaningfully lower compared to what reported in available literature. With an impressive 3.8% of dropouts our structured TAI methodology proved to provide results never achieved by previous authors, whose rates ranged from 13.3% to 39% (4,5,8,9,11,17-20,25). On this specific regard, we can speculate that a tailored indication for the water volume to be used during TAI administration represents the most significant improvement and peculiarity of our proposed methodology. The possibility to move to alternative, less invasive enemas (ultrasound or MRI based) could represent a further improvement of a really promising approach to the rehabilitation of patients with organic BD.

Larger prospective studies with validated measurements and standardized symptom-based outcome measures should be conducted to confirm our results and to further evaluate the utility of TAI in different settings including children with functional BD.

In conclusion, this clinical study focusing on TAI administered via Peristeen in a cohort of 78 children with organic-based BD has demonstrated the high efficacy of the innovative patient-tailored protocol. The results revealed significant improvements across all assessed scores, highlighting enhanced intestinal functionality and patient satisfaction. Importantly, it is worth noting that these improvements were observed in both patient groups, irrespective of the underlying cause of intestinal dysfunction. Notably, it became evident that the use of laxatives had a detrimental impact on several outcomes. These findings underscore the effectiveness of personalized TAI protocols and promote a safer and cautious use of laxatives in this patient population.

ACKNOWLEDGMENTS

The study was carried out at the following Italian hospitals: Alessandria (Pediatric Surgery, Umberto Bosio Center for Digestive Diseases, The Children Hospital, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo), Bergamo (Pediatric Surgery Unit, ASST Papa Giovanni XXIII), Firenze (Department of Surgery, Pediatric Urology Unit, Children's Hospital A. Meyer – IRCCS, University of Florence), Palermo (Pediatric Surgery, Azienda Ospedaliera Civico di Cristina Benfratelli), and Torino (Medium Intensity Surgery, O.I.R.M. Ospedale Infantile Regina Margherita A.O. Città della Salute e della Scienza).

The authors would like to thank the centers of Vicenza (Department of Pediatric Surgery and Pediatric Minimally Invasive Surgery and New Technologies, San Bortolo Hospital, Vicenza), Caltanissetta (Spina Bifida Centre, Azienda Sanitaria Provinciale), Pescara (Paediatric Surgery at the Civil Hospital), Cagliari (Paediatric Urodynamics, Azienda Ospedaliera G. Brotzu) who actively participated in the drafting the protocol and in the design of the study.

Special thanks are extended to the Staff-Nurse Anna Maria Amelotti of the Alessandria Centre for her active collaboration in managing patient data.

REFERENCES

1. Mosiello G, Safder S, Marshall D, Rolle U, Benninga MA. Neurogenic Bowel Dysfunction in Children and Adolescents. *J Clin Med*. 2021 Apr 13;10(8):1669.
2. Rajindrajith S, Devanarayana NM, Thapar N, Benninga MA. Functional Fecal Incontinence in Children: Epidemiology, Pathophysiology, Evaluation, and Management. *J Pediatr Gastroenterol Nutr*. 2021 Jun;72(6):794–801.
3. Choi EK, Shin SH, Im YJ, Kim MJ, Han SW. The effects of transanal irrigation as a stepwise bowel management program on the quality of life of children with spina bifida and their caregivers. *Spinal Cord*. 2013 May;51(5):384–8.
4. Ng J, Ford K, Dalton S, McDowell S, Charlesworth P, Cleeve S. Transanal irrigation for intractable faecal incontinence and constipation: outcomes, quality of life and predicting non-adopters. *Pediatr Surg Int*. 2015 Aug;31(8):729–34.
5. Mosiello G, Marshall D, Rolle U, Crétolle C, Santacruz BG, Frischer J, et al. Consensus Review of Best Practice of Transanal Irrigation in Children. *J Pediatr Gastroenterol Nutr*. 2017 Mar;64(3):343–52.
6. Baaleman DF, Wegh CAM, Hoogveld MTA, Benninga MA, Koppen IJN. Transanal Irrigation in Children: Treatment Success, Quality of Life, Adherence, Patient Experience, and Independence. *J Pediatr Gastroenterol Nutr*. 2022 Aug;75(2):166–72.
7. Bray L, Sanders C. An evidence-based review of the use of transanal irrigation in children and young people with neurogenic bowel. *Spinal Cord*. 2013 Feb;51(2):88–93.
8. Patel S, Hopson P, Bornstein J, Safder S. Impact of Transanal Irrigation Device in the Management of Children With Fecal Incontinence and Constipation. *J Pediatr Gastroenterol Nutr*. 2020 Sep;71(3):292–7.
9. Corbett P, Denny A, Dick K, Malone PS, Griffin S, Stanton MP. Peristeen integrated transanal irrigation system successfully treats faecal incontinence in children. *J Pediatr Urol*. 2014 Apr;10(2):219–22.
10. Emmanuel A. Review of the efficacy and safety of transanal irrigation for neurogenic bowel dysfunction. *Spinal Cord*. 2010 Sep;48(9):664–73.

11. Koppen IJN, Kuizenga-Wessel S, Voogt HW, Voskeuil ME, Benninga MA. Transanal Irrigation in the Treatment of Children With Intractable Functional Constipation. *J Pediatr Gastroenterol Nutr.* 2017 Feb;64(2):225–9.
12. Midrio P, Mosiello G, Ausili E, Gamba P, Marte A, Lombardi L, et al. Peristeen® transanal irrigation in paediatric patients with anorectal malformations and spinal cord lesions: a multicentre Italian study. *Colorectal Dis.* 2016 Jan;18(1):86–93.
13. López Pereira P, Salvador OP, Arcas JA, Martínez Urrutia MJ, Romera RL, Monereo EJ. Transanal irrigation for the treatment of neuropathic bowel dysfunction. *J Pediatr Urol.* 2010 Apr;6(2):134–8.
14. Furuta A, Suzuki Y, Takahashi R, Jakobsen BP, Kimura T, Egawa S, et al. Effects of Transanal Irrigation on Gut Microbiota in Pediatric Patients with Spina Bifida. *J Clin Med.* 2021 Jan 10;10(2):224.
15. Rendeli C, Paradiso VF, Bucci V, Creti G, D'Aleo C, Lisi G, et al. Gut microbiota and pediatric patients with spina bifida and neurogenic bowel dysfunction. *Childs Nerv Syst* [Internet]. 2022 Sep 30 [cited 2023 Mar 1]; Available from: <https://link.springer.com/10.1007/s00381-022-05688-0>
16. Caponcelli E, Meroni M, Brisighelli G, Rendeli C, Ausili E, Gamba P, et al. Transanal irrigation (TAI) in the paediatric population: Literature review and consensus of an Italian multicentre working group. *Pediatr Med Chir* [Internet]. 2021 May 7 [cited 2023 Mar 1];43(1). Available from: <http://www.pediatrmedchir.org/index.php/pmc/article/view/250>
17. Nasher O, Hill RE, Peeraully R, Wright A, Singh SJ. Peristeen Transanal Irrigation System for Paediatric Faecal Incontinence: A Single Centre Experience. *Int J Pediatr.* 2014;2014:1–4.
18. Pacilli M, Pallot D, Andrews A, Downer A, Dale L, Willetts I. Use of Peristeen® transanal colonic irrigation for bowel management in children: A single-center experience. *J Pediatr Surg.* 2014 Feb;49(2):269–72.
19. Van Renterghem K, Sladkov M, Matthyssens L, Van de Putte D, Pattyn P, Van Biervliet S, et al. Prospective switch study comparing two irrigation systems for transanal irrigation in children. *Acta Gastro Enterol Belg.* 2021 Jun;84(2):295–8.
20. Lallemand-Dudek P, Cretolle C, Hameury F, Lemelle JL, Ranke A, Louis-Borrione C, et al. Multicentric evaluation of the adherence to Peristeen® transanal irrigation system in children. *Ann Phys Rehabil Med.* 2020 Jan;63(1):28–32.
21. Costigan AM, Orr S, Alshafei AE, Antao BA. How to establish a successful bowel management programme in children: a tertiary paediatric centre experience. *Ir J Med Sci* 1971 -. 2019 Feb;188(1):211–8.

22. Caruso AM, Milazzo MPM, Bommarito D, Girgenti V, Amato G, Paviglianiti G, Casuccio A, Catalano P, Cimador M, Di Pace MR. Advanced Management Protocol of Transanal Irrigation in Order to Improve the Outcome of Pediatric Patients with Fecal Incontinence. *Children (Basel)*. 2021 Dec 11;8(12):1174. doi: 10.3390/children8121174.
23. Alhazmi H, Trbay M, Alqarni N, Alyami F, Khatab A, Almannie R, Neel KF. Long-term results using a transanal irrigation system (Peristeen®) for treatment of stool incontinence in children with myelomeningocele. *J Pediatr Urol*. 2019 Feb;15(1):34.e1-34.e5. doi: 10.1016/j.jpuro.2018.08.013. Epub 2018 Aug 28. PMID: 30245057.
24. López Pereira P, Salvador OP, Arcas JA, Martínez Urrutia MA, Romera RL, Monereo EJ. Transanal irrigation for the treatment of neuropathic bowel dysfunction. *J Pediatr Urol*. 2010 Apr;6(2):134-8. doi: 10.1016/j.jpuro.2009.07.004. Epub 2009 Aug 6.
25. Gordon T, Vandersteen DR, Dryjanski L, Carpenter J. Efficacy of Peristeen® transanal irrigation system for neurogenic bowel in the pediatric population. *J Pediatr Urol*. 2019 Dec;15(6):645.e1-645.e9. doi: 10.1016/j.jpuro.2019.09.023. Epub 2019 Oct 11.
26. Cazemier M, Felt-Bersma RJ, Mulder CJ. Anal plugs and retrograde colonic irrigation are helpful in fecal incontinence or constipation. *World J Gastroenterol*. 2007 Jun 14;13(22):3101-5. doi: 10.3748/wjg.v13.i22.3101. PMID: 17589927; PMCID: PMC4172618.
27. Rintala RJ, Lindahl H. Is normal bowel function possible after repair of intermediate and high anorectal malformations? *J Pediatr Surg*. 1995 Mar;30(3):491-4. doi: 10.1016/0022-3468(95)90064-0. PMID: 7760250.
28. Rintala RJ, Lindahl HG, Rasanen M. Do children with repaired low anorectal malformations have normal bowel function? *J Pediatr Surg*. 1997 Jun;32(6):823-6. doi: 10.1016/s0022-3468(97)90628-x. PMID: 9200078.
29. VISICK AH. A study of the failures after gastrectomy. *Ann R Coll Surg Engl*. 1948 Nov;3(5):266-84. PMID: 18112082; PMCID: PMC2238242.
30. Huskisson EC. Measurement of pain. *Lancet*. 1974 Nov 9;2(7889):1127-31. doi: 10.1016/s0140-6736(74)90884-8. PMID: 4139420.

Table 1 – Patients’ characteristics summary statistics ^a, N = 78. Of note, patients with Neurological issues leading to BD proved to be younger at enrollment with a reasonably lower autonomy in using the device.

Characteristic		Group		p-value	
		Overall N = 78	A (Organic causes) N = 44 (56.4%)		B (Neurological causes) N = 34 (43.6%)
ARM		29 (37.2)	17 (38.6)	12 (35.3)	-
Hirschsprung disease		15 (19.2)	15 (34.1)	-	-
Spina bifida		18 (23.1)	-	18 (52.9)	-
Other diseases		16 (20.5)	12 (27.3)	4 (11.8)	0.09
Sex	F	32 (41.0)	20 (25.6)	12 (15.4)	
	M	46 (59.0)	24 (30.8)	22 (28.2)	0.49
Age, months		106.1 (42.8) ^b	110.9 (38.8)	99.6 (47.5)	0.12
Height, cm		129.1 (21.9) ^c	135.5 (20.5)	122.0 (21.4)	0.009
Weight, kg		29.6 (14.0) ^d	32.8 (14.4)	25.2 (12.3)	0.006
Need for laxatives		46 (61.3)	29 (65.9)	17 (54.8)	0.35
Enema volume, mL		326 (200,400) ^e	355 (225,400)	285 (200,300)	0.06
Training duration, hours		1.45 (1.00,2.00) ^f	1.34 (1.00,2.00)	1.63 (1.00,2.00)	0.96
Location advice for TAI	Bed	12 (16.2)	8 (10.8)	4 (5.4)	
	Toilets	62 (83.8)	35 (47.3)	27 (34.5)	0.75
Autonomy	Using the device	33 (42.9)	24 (32.4)	9 (12.2)	0.03
	Filling the device	26 (33.8)	18 (24.3)	8 (10.8)	0.22
	Pumping water	19 (24.7)	11 (14.9)	8 (10.8)	1.00
	Catheter lubrication	18 (23.4)	12 (16.2)	6 (8.1)	0.43
	Catheter insertion	5 (6.6)	3 (4.1)	2 (2.7)	1.00

^a Statistics are: N (%) on non-missing counts for categorical variable, mean (SD or IQR) otherwise;

^b Min = 48, Max = 213; ^c Min = 95, Max = 174; ^d Min = 11, Max = 73; ^e mean (IQR), Min = 80, Max = 800; ^f mean (IQR), Min = 0.40, Max = 10;

Table 2 – Rintala Total Score Analysis. Continenence proved to improve significantly through timepoints. Multivariate analysis confirmed the negative effect on continence of laxatives in this patients' population.

Summary statistics for Rintala Total Score			
Timing	N	Mean (IQR)	Median
T0	78	7.8 (5.0,11.0)	7.5
T1	78	12.6 (10.0,15.0)	13.0
T2	75	13.8 (12.0,16.0)	14.0
T3	75	14.8 (14.0,17.0)	14.0
Univariate Repeated Measures Analysis for Rintala Total Score			
Factor	Comparison	Parameter Estimate β (SE)	p-value ^a
Timepoints	T1 vs T0	4.81 (0.37)	< 0.001
	T2 vs T0	6.13 (0.38)	< 0.001
	T3 vs T0	7.13 (0.38)	< 0.001
Group	B vs A	-1.22 (0.63)	0.05
Sex	M vs F	-0.80 (0.64)	0.21
ARM	Group A	-0.50 (0.74)	0.50
	Group B	0.06 (0.85)	0.95
Spina bifida	Yes vs No	-1.93 (0.75)	0.01
Autonomy (Yes vs No)	Device usage	0.39 (0.64)	0.54
	Filling	-0.22 (0.67)	0.74
	Water pumping	0.31 (0.73)	0.68
	Catheter lubrication	0.84 (0.74)	0.26
	Catheter insertion	1.76 (1.26)	0.16
Location for irrigation	Toilet vs bed	0.22 (0.86)	0.80
Laxatives	Yes vs No	-3.54 (0.53)	< 0.001
Enema volume		0.47 ^b (0.19)	0.01
Training duration		0.15 ^b (0.28)	0.59
Age		0.03 ^b (0.01)	< 0.001
Weight		0.07 ^b (0.02)	< 0.001
Height		0.05 ^b (0.01)	< 0.001
Multivariate Repeated Measures Analysis for Rintala Total Score			
Factor	Comparison	Parameter Estimate β (SE)	p-value ^a
Timepoints	T1 vs T0	4.61 (0.42)	< 0.001
	T2 vs T0	5.93 (0.44)	< 0.001
	T3 vs T0	7.11 (0.45)	< 0.001
Spina bifida	Yes vs No	-1.47 (0.79)	0.07
Laxatives	Yes vs No	-1.65 (0.47)	< 0.001
Enema volume		0.06 ^b (0.22)	0.78
Age		0.01 ^b (0.02)	0.86
Weight		0.01 ^b (0.05)	0.80
Height		0.01 ^b (0.05)	0.91

^a Type III Fixed effects F-test p-values; SE = Standard Error; ^b by 1 unit increase; SE=standard error; IQR=interquartile range

Table 3 – Frequency distribution of Rintala Score by Timepoints. It is clear how continence improves throughout timepoints with zero incontinence and 85% Good to Normal continence after 6 months of treatment.

Timing	N	Level, N (row %)			
		0-6 Poor	7-11 Fair	12-17 Good	≥18 Normal
T0	78	34 (43.6)	26 (33.3)	18 (23.1)	0 (0)
T1	78	6 (7.7)	18 (23.1)	50 (64.1)	4 (5.1)
T2	75	1 (1.3)	17 (22.7)	49 (65.3)	8 (10.7)
T3	75	0 (0)	11 (14.7)	49 (65.3)	15 (20.0)

Table 4 – Visick grade analysis. Patients' perspective of overall outcome proved to improve over time and in patients with larger volumes who did not use laxatives at enrollment.

Summary statistics for Visick grade by Time		Grade, N (row %)			
Timing (N)		I	II	III	IV
T1 (77)		37 (48.1)	26 (33.8)	11 (14.3)	3 (3.9)
T2 (75)		48 (64.0)	24 (32.0)	3 (4.0)	0
T3 (75)		62 (82.7)	12 (16.0)	1 (1.3)	0

VISICK Grade Univariate Repeated Measures analysis			
Factor	Comparison	OR (95%CI)	p-value ^a
Timepoints	T2 vs T1	5.67 (2.33,13.8)	< 0.001
	T3 vs T1	27.9 (8.47,91.7)	< 0.001
Group	B vs A	0.62 (0.20,1.89)	0.40
Sex	M vs F	0.49 (0.15,1.56)	0.22
ARM	Group A	0.80 (0.22,2.92)	0.74
	Group B	0.53 (0.12,2.26)	0.39
Spina bifida	Yes vs No	1.05 (0.26,4.28)	0.94
Autonomy	Device usage	1.04 (0.37,2.94)	0.94
	Filling	1.87 (0.64,5.49)	0.25
	Water pumping	0.97 (0.30,3.29)	1.00
	Catheter lubrication	0.95 (0.28,3.22)	0.94
	Catheter insertion	0.32 (0.03,3.19)	0.33
Location for irrigation	Toilet vs bed	1.71 (0.44,6.64)	0.44
Laxatives	Yes vs No	0.14 (0.05,0.37)	< 0.001
Enema volume		1.64 ^b (1.14,2.35)	0.008
Training duration		0.76 b(0.49,1.18)	0.22
Age		1.01 b(1.00,1.03)	0.05
Weight		1.04 b(1.00,1.09)	0.06
Height		1.03 ^b (1.01,1.06)	0.02

VISICK Grade Multivariate Repeated Measures analysis			
Factor	Comparison	OR (95%CI)	p-value ^a
Timepoints	T2 vs T1	3.84 (1.49,9.90)	0.006
	T3 vs T1	26.9 (6.93,105)	< 0.001
Laxatives	Yes vs No	0.15 (0.04,0.60)	0.008
Enema volume		2.18 ^b (1.21,3.90)	0.009
Height		1.01 ^b (0.98,1.05)	0.46

^a Type III Fixed effects F-test p-values; OR = Odds Ratio; CI = Confidence Interval; ^b by 1 unit increase.

Figure 1

Flow chart detailing the data collected during the visits of the study.

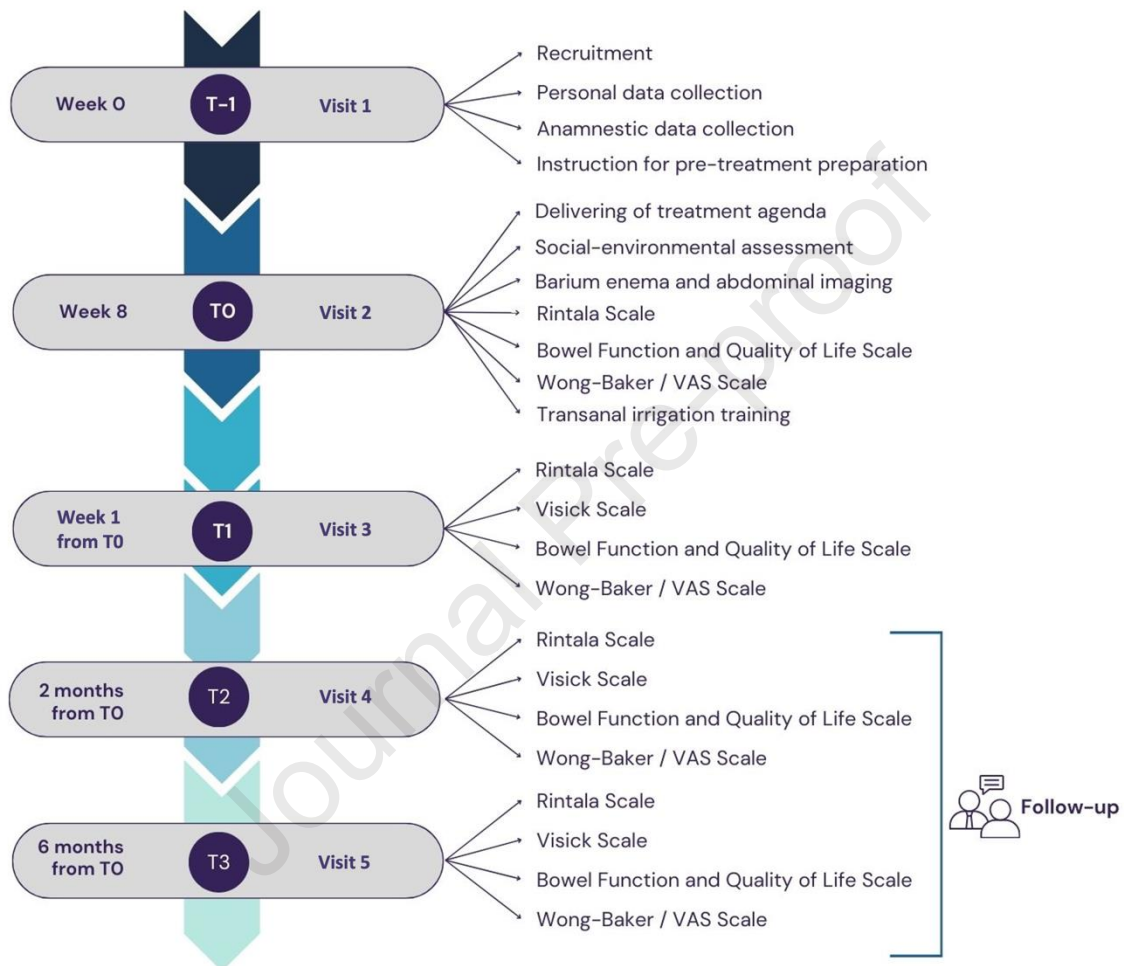


Figure 1

Rintala Total Score distribution by visit (**: p-values <0.001).

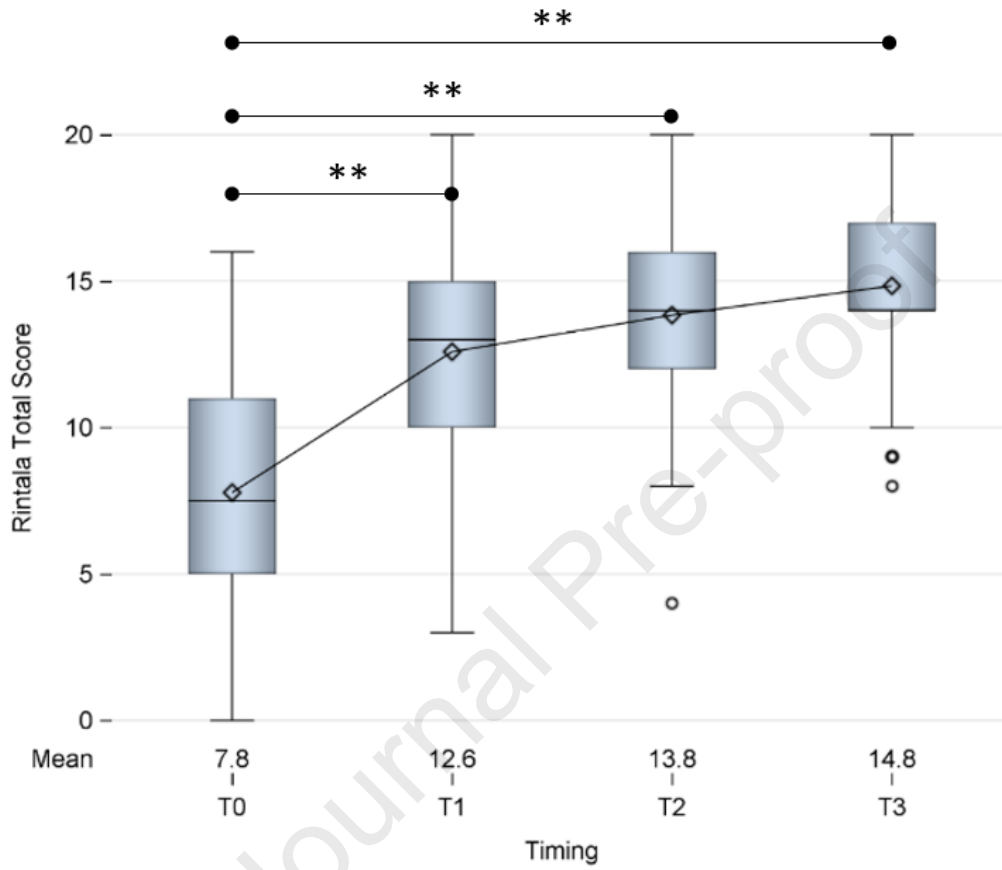
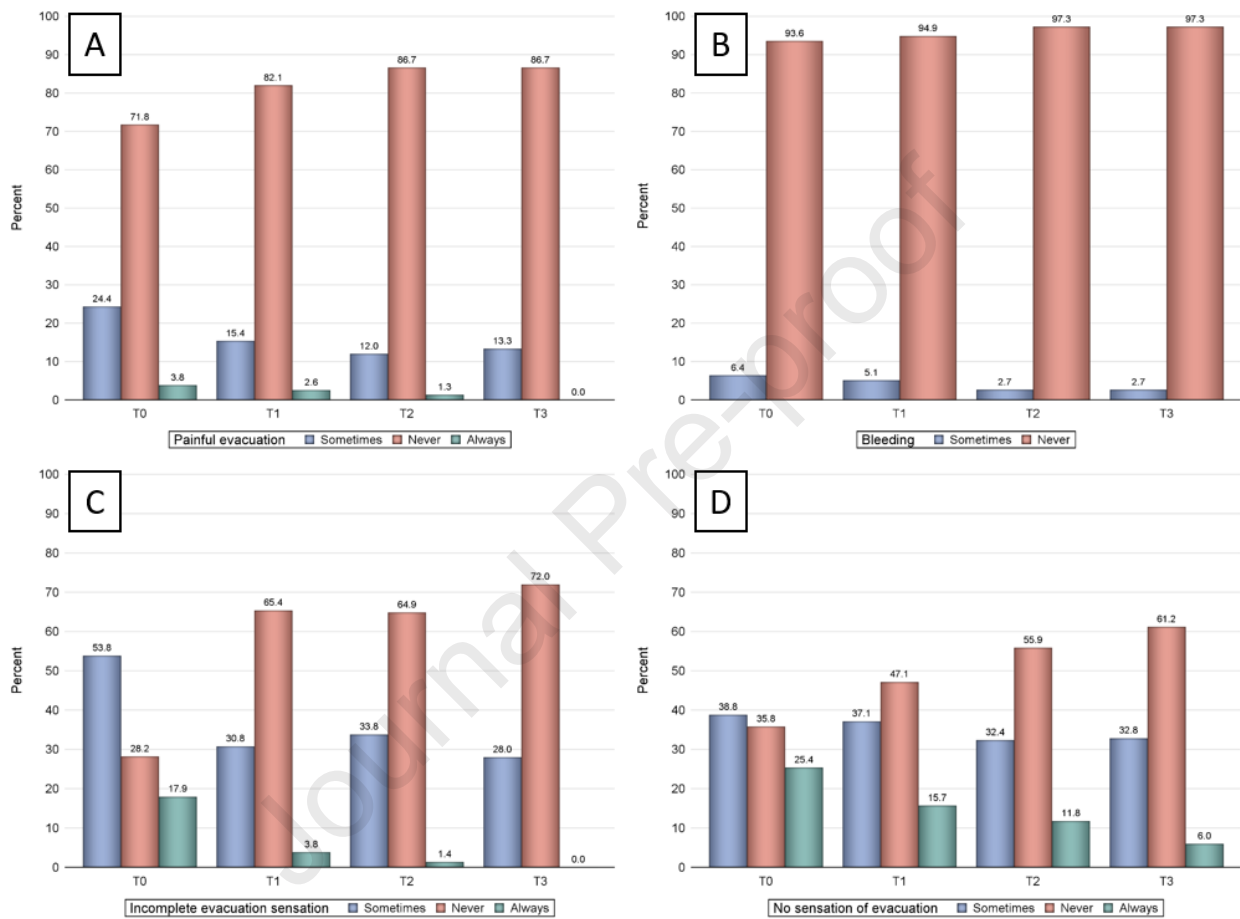


Figure 3

Graphical evidence of outcome measures, including *painful evacuation by time*, *bleeding by time*, *incomplete evacuation sensation by time*, *no sensation of evacuation by time*. All parameters demonstrated an improvement over time.



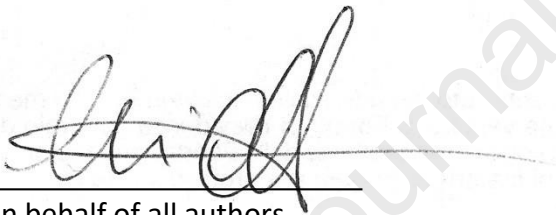
Authors Agreement

We declare that there are no known conflicts of interest associated with this publication. Coloplast supported meetings and travel costs during the implementation of the study, but this support was not significant and it did not influence the outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We take full responsibility for the work being reported. It is the original study and has been neither published elsewhere nor submitted for publication.

A handwritten signature in black ink, consisting of a series of loops and a long horizontal stroke, positioned above a solid horizontal line.

On behalf of all authors