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Behavioral outcomes of a novel, pelvic nerve damage rat model of fecal incontinence

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Abstract

Background: Fecal incontinence (FI) has a multifactorial pathophysiology with a severe social impact. The most common cause for FI is pudendal nerve damage, which mostly occurs in women during or after labor. A better understanding of the pathophysiology is required to optimize treatment of FI. In this study, we evaluate the use of a novel pelvic nerve damage rat model of FI.

Methods: This new model simulates the forces on the pelvic floor during labor by prolonged transvaginal, retro-uterine intrapelvic balloon distention in female rats. Number of fecal pellets produced per day and defecation pattern was compared between the experimental and control group for 2 weeks. The cages of the rats were divided in food, nesting and latrine areas to evaluate changes in defecation pattern. The FI Index (FII) was calculated to assess the ratio of fecal pellets between the non-latrine areas and the total number of pellets. A higher score represents more random distribution of feces outside the latrine area.

Results: Total number of fecal pellets was higher in the experimental group as compared with the controls. In both groups most fecal pellets were deposited in the nesting area, which is closest to the food area. The experimental group deposited more fecal pellets in the latrine area and had a lower FII indicating less random distribution of feces outside the latrine area.

Conclusion: Transvaginal, retro-uterine intrapelvic balloon distention is a safe and feasible animal model simulating the human physiologic impact of labor by downwards pressure on the pelvic floor.

KEYWORDS

fecal incontinence, pelvic nerve damage, rat model

1 | INTRODUCTION

Fecal incontinence (FI) is a multifactorial problem, with a severe social impact.¹ Several studies report a prevalence ranging from 7% up to 15% in adults that increases with age.² Obstetrical injury is the most common cause for FI.^{3,4} It is known that pudendal nerve damage is the most common cause for developing fecal incontinence.^{5,6} However, mechanisms of nerve damage remain uncertain. Due to its course

through the pelvic floor, this nerve is vulnerable for injury during labor such as traction at the level of the ischial spina, compression in the pudendal canal or avulsions of terminal fibers.⁷

Surgical treatment options for fecal incontinence can be divided into sphincter-restorative procedures, neuromodulation, neosphincter procedures and colostomy. Sphincter-restorative and neosphincter procedures are invasive procedures with low long-term success-rate of 40%^{8,9} and high complication rate ranging

up to 42%.¹⁰ Sacral neuromodulation (SNM) is a minimal invasive treatment option for FI with success-rates ranging from 47.7% up to 54% based on intention to treat analysis.¹¹⁻¹³ However, loss of efficacy occurs in up to 40% of patients treated with SNM.¹⁴ A common hypothesis is that the high rate of loss of efficacy of all treatment options for FI is often related to the lack of understanding of the pathophysiology of FI. Thus far, limited preclinical data on the pathophysiology of FI and associated behavioral changes have been reported.¹⁵⁻¹⁷ This is mainly due to the lack of reliable animal models in this field of research.

It is known that rats are a coprophagic species¹⁸ however, both the blind mole rats (*Spalax ehrenbergi*) and the normal rats are shown to exhibit place preference for its latrine to some extent.^{19,20} In this context, pudendal nerve transection in rats has been evaluated to assess the effect of neuropraxia on the external anal sphincter.^{16,21} Only one previous study has reported an animal model with pudendal nerve damage using retro-uterine balloon distention without traction to the pelvic floor.¹⁶ The model used an abdominal approach to place two retro-uterine catheters. Because the catheters were not fixated, it is debatable whether the correct pressure, comparable to labor condition was applied on the pelvic floor.

Here, we introduce a new animal model to study FI using objectified compressive forces on the pelvic floor that mimics the physiological pressure on the pelvic floor during vaginal delivery. We adapted a technique which was previously described by Sievert et al, to evaluate lower urinary tract after delivery in rats.²² However, this previous model used intravaginal balloon dilation, whereas we adapted this to transvaginal, retro-uterine, intrapelvic balloon distention. This model would facilitate a better insight in the pathophysiology of FI induced by obstetric trauma, which could change the treatment paradigm for FI.

2 | METHODS

2.1 | Subjects

This study was conducted on 16 adult virgin female Wistar rats (Charles River Laboratories, Sulzfeld, Germany). The animals were divided in two groups: an experimental group ($n = 10$) and a control group ($n = 6$). The experimental group underwent transvaginal, retro-uterine, intrapelvic balloon distention and the control group consisted of un-operated healthy controls. The experiments were approved by the Dutch Committee for Animal Research local ethical committee, Maastricht University (AVD107002015187; DEC 2015-001).

2.2 | Pressure calculation

Using a conversion calculator, we calculated that 100 mm Hg was equal to 0.013 N mm^{-2} .²³ The radius of the inflated balloon was 7.0 mm. The contact surface was $7^2 \times \pi = 153.94 \text{ mm}^2$. To imply a pressure of 100 mm Hg over the surface of the balloon (153.94 mm^2), we needed $0.013 \text{ N mm}^{-2} \times 153.94 \text{ mm}^2 = 2.05 \text{ N}$.

Key Points

- There's a lack of basic knowledge regarding the pathophysiology of fecal incontinence (FI).
- We introduce a new safe and feasible animal model for fecal incontinence with transvaginal, intra-pelvic balloon distention combined with downwards pressure on the pelvic floor.
- This is a validated model for future research regarding the pathophysiology of FI, that can be used to optimize the treatment paradigm.

For a force of 2.05 N on the pelvic floor, we required a freely hanging weight of $2.05/9.81 = 0.21 \text{ kg}$, which equals 200 g.

2.3 | Surgery

Ten rats underwent transvaginal, retro-uterine, intrapelvic balloon distention. Pre-operative analgesia was administered using Buprenorphine ($0.05 \text{ mg kg}^{-1} \text{ s.c.}$). Anesthesia was induced with 4%-5% Isoflurane (0.5 L per minute) in oxygen and maintained with 1.5%-3% Isoflurane. After successful anesthesia, the animals were placed in a supine position on a homeostatic warming blanket (Veterinary Technics/BDO-Medipass) to maintain a body temperature at 37°C . Next, a midline incision was made. The omentum and small intestines were positioned cranially. The cecum was lateralized to optimize visualization of the uterus. A pediatric urinary catheter (Ch. 8, Rüschi Brilliant Paediatric; Teleflex Medical Europe Ltd., Athlone, Ireland) was lubricated and inserted into the vagina and an incision was made on the dorsal part of utero-vaginal transition. The catheter was advanced through this incision and thereafter the balloon was inflated. The balloon had a maximum capacity of 3 mL. After inflation and correct positioning of the balloon, a weight of 200 g was attached to the end of the catheter, which hung freely from the operating table inducing a compressive force of 100 mm Hg on the pelvic floor (Figure 1). This force of 100 mm Hg is comparable to the pressure on the human pelvis during vaginal childbirth (range 100-240 mm Hg).^{24,25} Both during the operation as during the pressure induction, the abdominal cavity was protected from drought. The balloon was deflated after one hour of inflation and the intrapelvic part of the catheter was cut and removed abdominally to reduce further damage to the vaginal wound. The abdominal organs were checked and inspected for signs of hemorrhage and tissue damage and subsequently closed in layers using 2.0 Vicryl (fascia) and 3.0 monocryl (skin) (Ethicon). Afterwards, the animal was allowed to recover.

The animals in the control group were only anesthetized for the same time period as the animals in the experimental group. Anesthesia was induced with 4%-5% Isoflurane (0.5 L per minute) in oxygen and maintained with 1.5%-3% Isoflurane. After successful anesthesia, the animals were placed in a supine position on a homeostatic warming blanket (Veterinary Technics/BDO-Medipass) to maintain a body temperature at 37°C . Afterwards, the animal was allowed to recover.

FIGURE 1 (A-F) demonstrates the details of the surgical procedures. # the uterus; * the fallopian tubes; φ sigmoid; Λ the cervix; < the catheter tip at the cervix; ◊ the catheter tip; ψ the inflated catheter; ◀◀◀ the direction of the pressure induced on the pelvic floor

2.4 | Recovery

Postoperative pain medication was administered during 3 days follow-up using Caprofen 4-5 mg kg⁻¹ s.c. Rats were pair housed and were allowed to recover for 3 days with ad libitum access to food and water and housed in a temperature-controlled room with a 12-hour light-dark cycle. The recovery period was meant to reduce the risk of surgical stress-induced defecation abnormality in operated animals. Besides, all animals were weighed daily to ensure no significant weight loss occurred. Wounds were inspected daily. All animals tolerated the procedure well and no side-effects or complications occurred.

2.5 | Cage

A large rat cage with dimensions of 61 by 43.5 cm in length and breadth, respectively, was divided in three compartments (approximately 20 cm). Plates of five mm thick multiplex with a central doorway were used to create the compartments. The doorway allowed the rats to roam freely between the different compartments. The compartments consisted of area A, which contained the food and water, area B, which contained the majority of nesting and play materials and area C, which contained some nesting material (Figure 2). The division in three areas and allocation of the latrine area furthest from the food area is based on a previous study, which reported place preference for depositing fecal pellets as far away from the food area as possible.²⁰ By placing nesting material in the latrine area, rats should be interested in both areas and spent an equal amount of time in both. The floor of all three compartments was covered with sawdust. The rats could roam freely in the cage with

FIGURE 2 The cages were divided in three areas. This shows a typical distribution of the fecal pellets. Note: most pellets were found in the nesting area

a 12-hour light-dark cycle. Fecal pellets were counted per compartment every 24 hours, 5 days per week for 3 weeks. Notably, conventional cages were adapted and used for this proof of concept experiment. With this setting some difficulties occurred such as slight dislocation of dividing walls as it appears in the figure (Figure 2).

2.6 | Statistical analysis

Data are presented as standard error of the mean (SEM) for continuous variables, and count (percentage) for categorical variables. We calculated the Fecal Incontinence Index (FII) to assess the ratio of fecal pellets

between the non-latrine areas and the total number of fecal pellets.²⁰ A higher score represents more random distribution of feces outside the latrine area. The FII, total amount of fecal pellets and the proportion of fecal pellets per area were compared between the groups using repeated measures two-way (TIME and GROUP) ANOVA. The rule of outliers was applied for data which was ≥ 2 SE deviant from the mean. Statistical significance was defined as $P < .05$. Data were analyzed using SPSS (version 23 for Windows, IBM New York, USA).

3 | RESULTS

The surgical procedure was well tolerated by the operated animals. No complications such as peritoneal infection, gastrointestinal tract injury or intestinal ischemia were observed during or after surgery.

Moreover, no behavioral abnormalities that could have been linked to internal organ damage were observed. At autopsy, macroscopic inspection of the abdominal organs did not indicate any sign of internal damage. Besides, there was no weight loss in both groups over the course of the study. Furthermore, there was no weight differences between the groups at baseline (experimental 195.4 g [SE = 61.8]; controls 194.3 g [SE = 79.3]) ($P = .091$) and before sacrifice (experimental 211.3 g [SE = 66.8]; controls 214.3 g [SE = 87.5]) ($P = .26$).

During the study period of 14 days, the experimental group produced more fecal pellets per day (43.9 [SE = 0.63]) compared to the control group (40.8 [SE = 0.69]) (TIME effect $F = 21.18$, $P < .001$) (Figure 3). Besides, the experimental group deposited more fecal pellets in the latrine area than the control animals ($F = 2.15$; $P = .048$). This difference occurred for both the number of pellets in the latrine area as for the proportion of pellets in the latrine area compared to the total number of pellets in the cage. However, in contrast with the expected effect, both groups deposited most of the fecal pellets in the nesting area (Figure 4). The proportion of fecal pellets in the nesting and latrine area compared to the total amount of fecal pellets remained stable during follow-up in both groups.

The FII was lower in the experimental group compared with the control group during follow-up (TIME by Group effect, $F = 2.15$; $P = .048$), illustrating a change in defecation behavior after surgery (Figure 5). Animals in the experimental group deposited more fecal pellets in the latrine area compared to the controls suggesting that

healthy animals do not have a place preference for defecation as previously suggested.²⁰

4 | DISCUSSION

This study demonstrates that transvaginal, retro-uterine intrapelvic balloon distention is a safe and feasible model for induction of FI in rats. Besides, the three-area cage model allows easy evaluation of defecation pattern and possible changes in defecation behavior after surgery. Animals in the experimental group deposited more fecal pellets in total (TIME effect) and dropped more fecal pellets in the latrine area compared to the healthy controls. The FII was lower in the experimental group, suggesting a less random distribution of fecal pellets compared to the healthy controls (TIME by GROUP effect).

Animals in the experimental group produced more fecal pellets during follow-up compared with the control group. To our knowledge, only one previous study assessed defecation behavior in healthy rats too.²⁰ They reported a mean total daily amount of fecal pellets of 43 (range 28–59), which is comparable to the total daily amount of fecal pellets of both our experimental and healthy groups. However, results should be compared with caution as their study had a limited follow-up of only 4 days. Our results showed a higher mean number of fecal pellets in both groups during the first week, which decreased as follow-up continued. The comparable amount of fecal pellets reported by Soetan et al²⁰ might be due to a stress-component. It was previously reported that defecation frequency increases after inducing stress by placing rats in a different environment.²⁶

Most fecal pellets were deposited in the nesting area by both the experimental and control group. Previous studies have shown a place preference far away from the feeding area for deposition of fecal pellets in rats.^{19,20} One study also divided the cages in three areas (food, nesting and latrine areas) but included only healthy rats.²⁰ In contrast to our results, Soeten et al reported most fecal pellets were deposited in the latrine area during a follow-up of only 4 days.²⁰ This difference in place preference is most likely related to differences in the experimental settings because our results after 4 days showed that both groups also deposited most fecal pellets in the nesting area. In a very recent study, the same group has replicated their finding using a well-designed video-tracking behavioral study, showing that this model of

FIGURE 3 Total amount of fecal pellets produced per day. The experimental group produced more fecal pellets per day according to repeated measures two-way ANOVA (TIME effect $F = 21.18$, $P < .001$). Values are presented as standard error of mean (SEM)

FIGURE 4 Proportion of fecal pellets per area compared to the total amount of fecal pellets in the cage. The experimental group deposited more fecal pellets in the latrine area compared to the control animals ($F = 2.15$; $P = .048$). Values are presented as standard error of mean (SEM)

pudding neuropathy affects continence in 32% of rats.²⁷ There were several differences in the experimental setting between our study and Soetan et al²⁰ Firstly, we used larger cages to allow the animals more movement freedom. Secondly, our cages were divided using dark multiplex walls instead of see-through Plexiglas walls. Moreover, we pair housed the animals instead of solitary housing. Finally, we also placed nesting material in the latrine area instead of only placing it in the nesting area. We hypothesized that if place preference was related to a behavioral mechanism to deposit feces as far away from the food as

possible, nesting material should not be of influence. By placing nesting material in the latrine area, rats should be interested in both areas and spent an equal amount of time in both. Due to logistical limitations we did not track the time the animals spent in each area. This limitation prevents a correlation between time spent in each area and amount of fecal pellets deposited in that area.

In contrast with what we expected, the Fecal Incontinence Index was lower in the experimental group during follow-up indicating that the experimental group deposited less fecal pellets outside the

FIGURE 5 Fecal Incontinence Index. The experimental group had a significant lower FI according to two way repeated measures ANOVA ($F = 2.15$; $P = .048$). Values are presented as standard error of mean (SEM)

latrine area compared to the healthy controls. The healthy controls deposited more fecal pellets in the non-latrine areas compared to the experimental group indicating a more random distribution in healthy animals. It is hypothesized that although rats do not display a place preference for depositing fecal pellets, an anxiety component after surgery cannot be excluded. Feeding and coprophagic behavior can be excluded as a potential cause as all animals had unrestricted access to food and water. Also, it has been previously shown that the distribution of feces is not influenced by collection of pellets for coprophagic purposes.²⁰

This work shows that only 30% of our rats develop incontinence and therefore the authors new method may prove superior in the future.²⁷ For further validation of this method, we suggest histological studies on acute and long-term effects of transvaginal, retro-uterine balloon distention on the muscle mass of the anal sphincter complex. A previous study reported loss of muscle mass of the external anal sphincter after application of a comparable technique.¹⁶ Loss of muscle mass 1 week after balloon distention was comparable to the muscle loss 1 week after bilateral pudendal nerve crush lesions. However, loss of external anal sphincter muscle mass was recovered 4 weeks after balloon distention. Recovery of neural damage in rats has previously been reported by studies in the field of experimental neuronal damage models.²⁸⁻³⁰ They showed that neuroplasticity in the subcortical regions in rats allows recovery from stroke and spinal cord injuries through neural remodeling. The immunohistochemical analysis of this study was limited by the absence of an evaluation of the anal sphincter complex. Moreover, the effect of environmental factors such as stress or anxiety on defecation behavior yet to be verified in this animal model.

This study demonstrated that transvaginal, retro-uterine, intrapelvic balloon distention is a safe and feasible animal model for induction of fecal incontinence simulating the human physiologic impact of labor. This is a valid model for future research regarding the pathophysiology of FI, which can be used to optimize the treatment paradigm and explore novel therapeutic approaches.

CONFLICT OF INTEREST

PJ, SB, and JM received a non-restrictive research grant from Medtronic.

AUTHOR CONTRIBUTIONS

PJ, SB, JM, LS, NB, YT, and AJ designed the study; PJ and AJ performed the surgeries and collected the data; PJ, SB, YT, and AJ analyzed and interpreted the data; PJ, SB, JM, LS, NB, YT, and AJ drafted the manuscript; LS, NB, YT, and AJ supervised the study. All authors gave final approval of the final version.

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