

Article

Rectal Prolapse in Laboratory-Housed Macaques: Assessing Prevalence, Risk Factors, and Enhanced Treatment Modality

Julie Leleu ¹, Maxime Simon ¹ , Luiz Cesar Cavalcanti Pereira da Silva ², Tommaso Virgilio ³ ,
Melissa A. de la Garza ⁴  and Jaco Bakker ^{5,*} 

¹ VetAgro Sup, Veterinary School, 69280 Marcy L'Etoile, France; julie.leleu@vetagro-sup.fr (J.L.); maxime.simon@vetagro-sup.fr (M.S.)

² Institute of Science and Technology in Biomodels, Fiocruz, Rio de Janeiro 21040-900, Brazil; luiz.cavalcanti@fiocruz.br

³ Institute for Research in Biomedicine, Università della Svizzera Italiana, 6500 Bellinzona, Switzerland; tommaso.virgilio@irb.usi.ch

⁴ University of Texas MD Anderson Cancer Center, Michale E. Keeling Center for Comparative Medicine and Research, Bastrop, TX 78602, USA; made4@mdanderson.org

⁵ Animal Science Department, Biomedical Primate Research Centre, 2288 GJ Rijswijk, The Netherlands

* Correspondence: bakker@bprc.nl

Abstract: Rectal prolapse is a common condition in laboratory-housed macaques, usually associated with recurrent gastroenteritis and stress. However, evidence for both statements is lacking. Therefore, the prevalence of rectal prolapses and their risk factors in laboratory-housed macaques have yet to be assessed. In addition, a standard of care pharmacological treatment remains to be recognized and documented. Thus, a retrospective study involving 816 laboratory-housed macaques was conducted, in which the prevalence, risk factors, and treatment success of rectal prolapses was assessed. The prevalence was shown to be 3.92%, and all cases could be either directly or indirectly linked to stress factors. By eliminating the suggested stressor, most rectal prolapses reverted naturally (69%). Moreover, we discuss the advantage of the ancillary administration of hyoscine butylbromide and metamizole as a treatment modality.

Keywords: rectal prolapse; macaques; treatment; manual reposition; metamizole; hyoscine butylbromide; prevalence; stress; etiology; risk factor



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1. Introduction

Rhesus (*Macaca mulatta*) and cynomolgus macaques (*Macaca fascicularis*) are among the most frequently used non-human primate (NHP) species in biomedical research. Although born and raised in captivity, macaques retain their natural instincts and behave as undomesticated wild animals. They are susceptible to stress and injury, particularly during capture, chemical or physical restraint, and handling for sample collection or routine care [1,2]. Training macaques to participate in experimental procedures such as venipuncture, entering a transport box, and presenting the hind leg for injections with positive reinforcement training (PRT) can reduce stress responses [3–5]. Nevertheless, even straightforward procedures such as anesthesia, transport, or other changes to their routine, as well as similar procedures occurring in the vicinity can still be distressing to macaques [6,7].

Overexposure to chronic or acute stress is known to cause several physical, emotional, and behavioral responses [8], to alter the physiology of the animal, and to induce diseases, including, among others, rectal prolapse (RP) [9,10]. RPs have been reported in humans and a variety of animals, including domestic dogs and cats, mice, swine, calves, and several primate species, such as vervet monkeys (*Chlorocebus pygerythrus*), Sumatran orangutans (*Pongo abelii*), olive baboons (*Papio anubis*), Sulawesi crested black macaques (*Macaca nigra*), black-crested mangabeys (*Lophocebus aterrimus*), mountain gorillas (*Gorilla beringei*

beringei), and cynomolgus macaques [7,8,11–21]. In humans, RPs have an annual incidence of 2.5 cases per 100,000 people [22]. RPs can occur in children and adolescents [23–26]. In laboratory-housed macaques, RPs are described to be commonly observed in stressed animals, especially in association with recurrent gastroenteritis. RPs are described as affecting animals of any age and sex but are most frequently observed in young animals [11,27–29]. However, supporting data for their statements are not provided by these authors. Thus, the detailed prevalence of RPs and their etiology in laboratory-housed macaques are currently unknown. A retrospective study of zoo-housed Sulawesi crested black macaques conducted over a 7-year period, involving 204 animals, showed that 12.3% of the animals suffered from at least one RP event during the study period [9].

The initial evaluation of a macaque affected by RP should preferably include a complete history and physical examination, with a focus on the prolapse, on anal sphincter structure and function, and on concomitant symptoms and underlying conditions. RP corresponds to an eversion of one or more layers of the rectum through the anus. It may be partial, involving an externalization of the rectal mucosal tissue only, or complete, if presenting as a cylindrical protrusion of all the layers of the rectal tissue [28–30]. In human medicine, multiple treatment modalities have been described depending on the grade of the RP which significantly improved upon over time, e.g., injection sclerotherapy and anal encirclement, in addition to surgical rectopexy by open and newer minimally invasive methods [23–26]. In macaques, RPs often resolve naturally inside the anus after the removal of the stressor [27,28]. If the RP does not revert naturally, and the mucosa is still viable and without lacerations, manual reduction is required. In case of edema of the prolapsed rectum, hypertonic compresses and purse-string sutures may be indicated to prevent recurrence [28]. The purse-string suture should be placed through the skin and the deep fascia around the anus where one finger can be passed through the anus. The knot needs to be tied in a bow to facilitate suture removal. When a purse-string suture fails to stop recurrence, and while the rectal tissue is still vital, colopexy is indicated [13]. More severe cases, associated with infection, necrosis, or irreversible trauma of the prolapsed rectum, may necessitate the resection of damaged tissues in conjunction with a perianal purse-string suture to prevent recurrence of the disease [28]. In severe cases, euthanasia may be indicated [9]. RP symptoms are suggested to include pain and discomfort felt deep within the lower abdomen [20,23–26]. Therefore, appropriate analgesic use is mandatory for guaranteeing the welfare of the animals.

Generic formulations consisting of a combination of hyoscine butylbromide and metamizole are globally commercially available. These formulations are a combination of an antispasmodic (spasmolytic) and anticholinergic drug, which are described to suppress spasms of the digestive system [31–39]. They act directly in the abdomen, targeting and relieving the cause of abdominal pain, and are indicated for the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic, and simple impactions in cows, pigs, dogs, and horses [40–43]. Metamizole possesses anti-inflammatory, antipyretic, and analgesic properties by counteracting the inflammation of the intestine, resulting from any enteritis mediated by endo- or enterotoxins [37–39]. The administration of this drug for RP in macaques has not been described in the literature, yet while its application may be beneficial.

To fulfill this lack of knowledge, a retrospective study was conducted to assess the prevalence and risk factors of RPs in laboratory-housed macaques. In addition, the administration of an antispasmodic (spasmolytic) and anticholinergic drugs, i.e., hyoscine butylbromide and metamizole, was envisaged as an enhanced treatment modality.

2. Material and Methods

2.1. Animals, Husbandry and Housing

The Biomedical Primate Research Centre (BPRC, Rijswijk, The Netherlands) housed an outbred breeding colony of rhesus and cynomolgus macaques. The animals were grouped in multigenerational families in enriched enclosures, consisting of freely accessible indoor and outdoor compartments. Wood fiber bedding was provided on the floor of the indoor enclosures, while the outside enclosures consisted of sand bedding. Removal of feces from the outside enclosures and intensive cleaning of the inside enclosures occurred monthly. Environmental enrichment consisted of several climbing structures, beams, fire hoses, and sitting platforms. Indoor enclosure temperature was maintained at approximately 18 °C and 21 °C for rhesus and cynomolgus macaques, respectively, with a 12:12 h light–dark cycle. The macaques were fed commercial monkey pellets (Ssniff, Soest, Germany) supplemented with limited amounts of fruit and vegetables. Water was available *ad libitum*, provided by automatic water dispensers.

Qualified animal caretakers observed all animals at least twice daily for injuries and illnesses. All animals were housed in accordance with Dutch law and international ethical and scientific standards and guidelines. All husbandry procedures were compliant with the above standards and legislation. Animal care at BPRC is in accordance with programs accredited by AAALAC International. No animals were captured and sedated solely for the purpose of this study. Therefore, ethical approval was not required for this study.

2.2. Study Design and Data Collection

Retrospective data were obtained from the electronic health record database of the BPRC. The dataset used for the analysis covered the period from 1 January 2023, to 31 December 2023. Data were analyzed on the presence of RPs, clinical features of the RP, and associated risk factors such as stress due to capture, handling, and chemical restraint or a history of episodes of diarrhea, idiopathic chronic diarrhea, or gastrointestinal (GI) infections. The database contained detailed health records from each individual animal, including results of the bacteriological and parasitological screening.

Detailed recommendations about enhanced treatment modalities and interventions in macaques are lacking in the literature [27,28]. As RP symptoms are suggested to include pain and discomfort felt deep within the lower abdomen [23–26,44], appropriate analgesia was applied at the BPRC in the form of hyoscine butylbromide and metamizole. This enhanced treatment modality was evaluated by scoring the number of recurrences of RP after treatment. Assessment of pain and pain relief after treatment was not included.

We monitored a total of 816 macaques, including 187 cynomolgus macaques (89 males and 98 females) ranging from 8 months to 22 years, and 629 rhesus macaques (218 males and 411 females) ranging from 6 months to 22 years.

3. Results

The characteristic clinical sign of RP besides exteriorization of the rectum was the typical posture: elevated hindquarters with the head lowered, accompanied by a small amount of blood mixed with feces adhering to the perineal and tail region.

In total 32 RPs were observed, resulting in a prevalence of 3.92% (32/816) (Table 1). Of the 32 observed RPs, 11 occurred during isolation, handling, and capture. Those 11 cases involved ten rhesus macaques (five males and five females: one 16-year-old, three 3-year-olds, two 2-year-olds, three 1-year-old, and one 7-month-old) and one 6-year-old male cynomolgus macaque. All remaining 21 cases could be directly or indirectly linked to a social or environmental stressor (e.g., catching animals in neighbored groups, introducing a new breeding male into a group or neighboring groups, locking macaques outside for cleaning the inside enclosures). Those 21 cases involved one female cynomolgus and 20 rhesus macaques (seven males and 13 females).

Table 1. The number of animals in the colony at risk for rectal prolapse, the number of observed rectal prolapses, the number of treated animals, the number of naturally reverted prolapses after removal of the stressor, and the number of observed recurrences.

Number of Animals	Number of Rectal Prolapse	Number of Treated Animals	Naturally Resolved Rectal Prolapses	Number of Observed Recurrences
816	32	10	22	0

By eliminating the suggested stressor, 22 RPs of the 32 RPs (69%) reverted spontaneously (Figure 1a). The health records showed that no RPs were associated with GI infection or episodes of diarrhea. No macaques suffering from chronic idiopathic diarrhea experienced RPs. In ten cases, manual reduction was performed after sedation of the macaque (Figure 1b). First, the prolapsed mucosa was rinsed with warm saline. Subsequently, fingers were used to gently push the prolapsed mucosa back in through the anus, to place back the prolapsed bowel into its normal anatomical position (Figure 2a–d). In addition, in those ten macaques, hyoscine butylbromide and metamizole (i.e., Buscopan® Compositum; Boehringer–Ingelheim), were ancillary administered intramuscularly (IM) to reduce abdominal pain, at a dose of 0.20 mg hyoscine butylbromide and 25 mg metamizole sodium per kg body weight. No purse-string sutures were used. No nonreducible or severely traumatized RPs were observed, i.e., no surgical resections were performed, and no macaques were euthanized. No cases of recurrence of RP after treatment was observed.

The breeding colony provided purpose-bred research animals, resulting in a skewed age and sex distribution in the colony. In addition, the number of observed RPs showed a wide-spread age range. Therefore, a correlation analysis, which would normally be used to study the relationship between RP occurrence and age and sex, was not performed, as that would result in inaccurate and misleading results.



Figure 1. Examples of rectal prolapses attributed to stress in macaques: (a) A macaque squeezed to administer a sedative. Rectal prolapse occurred, which reverted naturally after removal of the stressor; (b) Example of a rectal prolapse which needed manual reduction by a veterinarian (photographs provided by Biomedical Primate Research Centre).

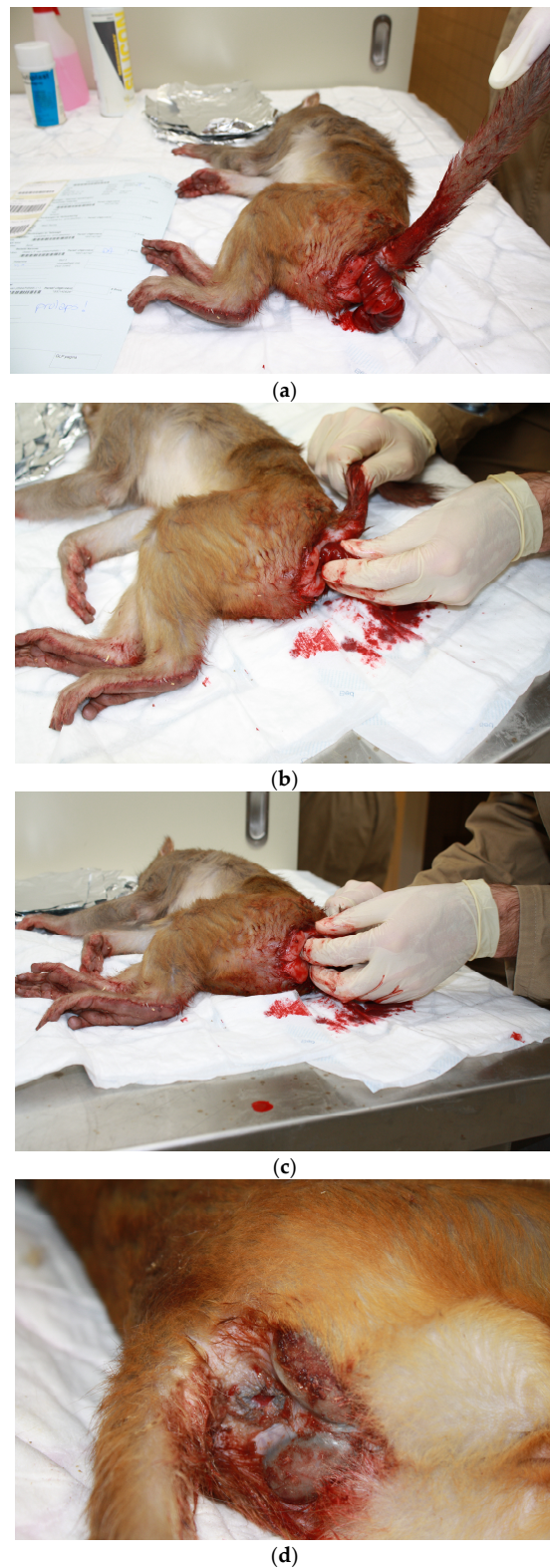


Figure 2. Example of a rectal prolapse with viable rectal tissue which did not revert naturally. (a) Rhesus macaque showing a rectal prolapse; (b) after washing with warm saline, manual reposition was performed; (c) fingers were used to gently push the prolapsed mucosa back in through the anus, to place back the prolapsed bowel into its normal anatomical position; (d) prolapse reverted (photographs provided by the Biomedical Primate Research Centre).

4. Discussion

In our retrospective study, a stressor was associated with all the cases of RPs. The assessed prevalence of RPs was shown to be 3.92%. No cases or RPs were associated with GI infections, episodes of diarrhea, or chronic diarrhea. Removing the stressor induced the natural reversion of the RPs in 69% of the cases.

Stress is a recognized risk factor for recurrent RP both in humans [23–26,44,45] and in NHPs [9,10,28,29]. In our study, all cases could be either directly or indirectly linked to a stressor, e.g., isolation and capturing, catching animals in neighbored groups, introducing a new breeding male into a group or neighboring groups, locking macaques outside for cleaning the inside enclosures. New males and resident females are described to experience high stress levels during an introduction of a new breeding male into an established social group, similar to male group entry in the wild [46–48]. Our results seem to confirm those observations.

A stressor was reported in 64% of the cases of RP within 1 month prior to RP events (prevalence 12.3%) in zoo-housed Sulawesi crested black macaques [9]. At the BPRC, efforts were made to minimize stress during capture procedures, before sedation. As the BPRC is well-experienced and progressive in refinement, a continuous training program was developed to establish cooperation during the capture procedure in the group-housed macaques (PRT). As part of this training program, animals were trained to voluntarily enter individual squeeze cages. This training may have contributed to the observed prevalence of 3.92% of RPs at the BPRC, further supporting the relevance of stress as the etiology of RPs in laboratory-housed macaques. The stressors described in zoo-housed Sulawesi crested black macaques included group aggression and interventions, involving restraint or transport of animals. The majority of RPs reverted naturally, but 28% of afflicted animals were euthanized for this ailment [9]. At the BPRC, no macaques were euthanized. Moreover, zoos with high frequencies of diarrhea and those with more male than females were described to have increased odds of developing RPs [9]. Interestingly, all our RPs observed, were not associated with GI infections or recurrent gastroenteritis. Moreover, zoos that provided diets of 90% vegetables and high-fiber pellets were described as also having increased odds of developing RPs. These findings could indicate either a lack or an excess of nutritional components in their diets, predisposing Sulawesi crested black macaques to RPs. The relatively low prevalence at the BPRC could be related to the diet provided at the BPRC, which was described to be optimized [49]. This should be interpreted with caution before altering feeding practices in zoos, as changing diet can increase the incidence of morbidities, such as diabetes, and because other husbandry variables, genetic elements, and influence of zoo visitors cannot be excluded as confounding factors. Consequently, no conclusions can be drawn without in-depth dietary analyses.

RPs are described to result from tenesmus or increased intra-abdominal pressure, such as straining, which can be the consequences of chronic diarrhea, neoplasia of the rectum or distal colon, cystitis, urolithiasis, prostatitis, rectal foreign bodies, pregnancy, dystocia, or lacerations [12,23–26,28–30,44,50]. RPs have also been hypothesized to be caused by laxity or weakness of the pelvic floor muscles, which is often associated with childbearing in women. However, 50% of women with RP have been reported to be nulliparous and this hypothesis also does not explain the incidence of RPs in men [51]. In laboratory-housed macaques, RPs are attributed to either parasitic or bacterial infections and consequent colitis, or to relevant stress-inducing events [11,27–29,52]. However, those authors do not present evidence for their statements.

The mechanism of action of hyoscine butylbromide and metamizole does not directly suggest a possible application for stress-related RPs [31–43]. However, two reports described a similar strategy as ours for the treatment of RP in calves [12,53]. In these cases, hyoscine butylbromide was administered at a dose rate of 0.4 mg/kg IV to control contractions of GIT smooth muscle and, thus, tenesmus.

One of the top priorities in a research facility is maintaining a high level of animal welfare. Hyoscine butylbromide and metamizole contain analgesic properties. A reduction

in abdominal pain may decrease the abdominal pressure, while the spasmolytic effect reduces the initial tenesmus, eventually reducing the probability of RP recurrence. For these reasons, hyoscine butylbromide and metamizole were introduced as a treatment modality for RPs at the BPRC. Unfortunately, assessing pain in the group-housed NHPs, such as in our breeding colony, is hard, and was therefore not included in our study [54,55].

Use of hyoscine butylbromide and metamizole in macaques is off label; thus, doses are extrapolated from other species. At the BPRC, hyoscine butylbromide and metamizole were administered at doses recommended for pigs and cows: 0.20 mg hyoscine butylbromide and 25 mg metamizole sodium per kg bodyweight. Overdosing of hyoscine butylbromide is not reported to cause constipation, as hyoscine butylbromide primarily targets smooth muscle spasms. Drug overdose may lead to anticholinergic symptoms such as urinary retention, dry mouth, reddening of the skin, tachycardia, inhibition of gastrointestinal motility, and transient visual disturbances may occur (<https://www.medicines.org.uk/emc/files/pil.890.pdf>; accessed on 1 August 2024). We did not observe signs of overdosing.

Recommendations for postoperative care of RPs in humans include an NSAID, an analgesic, and an osmotic laxative (polyols, polyethylene glycol) [23–26,44,45]. Metamizole is described to be less frequently associated with neurological adverse effects than opioids and to have a better neurological side effect profile than NSAIDs [56,57]. Overall, for short-term use in the human hospital setting, metamizole seems to be a safe choice when compared to other widely used analgesics such as paracetamol and acetylsalicylic acid. In addition, it should be noted that macaques may not be able to complete certain treatment regimens, as it may be difficult to apply local treatment for several consecutive days. Accessing the rectal area is not feasible without sedation, and injections would cause stress due to the need for restraint. In addition, the manipulation involved may also stress other macaques in the vicinity. In addition, macaques are notorious for refusing medicated food. Furthermore, the established hierarchy of a rhesus colony involves social conflicts that often lead to aggression and may result in severe wounding. Separating an animal from a group for treatment can exacerbate these social conflicts. Unfortunately, long-acting NSAIDs and analgesics, which would significantly reduce unnatural social disturbance, are not currently available in Europe for primates. In the US, extended-release formulations (up to 72 h) of meloxicam and buprenorphine are used off-label, but both have been implicated as causing abscesses, and the buprenorphine extended-release injection is not even currently available [58,59]. Therefore, hyoscine butylbromide and metamizole may be considered as integral components of a therapeutic package for the treatment of RPs in macaques.

5. Conclusions

In our retrospective study, a stressor could be directly or indirectly linked with all the cases of RPs that we observed. The prevalence of RP was shown to be 3.92%. No cases of RP were associated with GI infections or chronic diarrhea. Removing the stressor induced natural reversion in 69% of the observed RPs. However, in some cases, the RPs needed to be manually reduced. Our empirical experience, supported by other reports, indicates that in those cases the adjunctive administration of hyoscine butylbromide and metamizole might be beneficial to the welfare of the animal. Thus, the current study not only describes, for the first time, the prevalence of RPs in laboratory-housed macaques but also advocates for the ancillary administration of hyoscine butylbromide and metamizole after the manual repositioning of the RPs in laboratory-housed macaques.

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