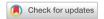
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Prevalence and treatment of gastric ulcers in Thoroughbred racehorses of Korea

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ABSTRACT

Background: Gastric ulcer is one of the prevalent diseases in racehorses. However, it has not been recognized as important in Korea, and drugs used to treat gastric ulcers are included in the doping test list, so they are not allowed to be administered to racehorses in training.

Objectives: This study was performed 1) to investigate the prevalence and the severity of gastric ulcers in Thoroughbred racehorses in Korea, 2) to confirm the therapeutic effect of ranitidine and omeprazole, and 3) to compare the efficacy between ranitidine and omeprazole.

Methods: Forty-nine horses were randomly recruited, and gastroscopy was performed within two days after racing. Twelve horses with a sum grade of five or higher were randomly assigned to two treatment groups. Seven horses were administered ranitidine, and five horses were administered omeprazole. Follow-up gastroscopy was scheduled within one to five days after finishing the treatment.

Results: The prevalence of gastric ulcer in Korean Thoroughbred racehorses after racing was 100%, and the grade was more severe in the non-glandular region than in the pyloric region. There was no correlation between the severity of gastric ulcer in the two regions. Omeprazole had a greater therapeutic effect than ranitidine.

Conclusions: This study shows the importance of recognizing gastric ulcers as an important factor, and omeprazole as a possible treatment option in Korea, as it has been removed from the list of prohibited substances for racehorses. Thus, the use of omeprazole is currently recommended until one day before the race.

Keywords: horses; gastric ulcer; prevalence; ranitidine; omeprazole

INTRODUCTION

Gastric ulcers are a significant problem in horses, particularly in racing horses. Horses with gastric ulcers have clinical signs such as weight loss, inappetence, poor coat condition, colic, changes in behavior, poor performance or failure to train up to expectations, and poor body condition [1-4]. Previous studies have reported that more than 70% of horses in race training have gastric ulcers [5-7], and up to 100% of horses have gastric ulcers if they are in active

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Conflict of Interest

The authors declare no conflicts of interest.

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race training [8-12]. It is estimated that Korean racehorses participating in racing at intervals of 2–6 weeks may experience a high prevalence of gastric ulcers. As such, corresponding investigations should be conducted.

Various methods can be used to prevent and treat gastric ulcers, and it is necessary to evaluate efficacy of currently used drugs and efficiency of administration methods. In addition, when participating in training and racing in an environment in which gastric ulcers are expected, it is necessary to prepare ways to prevent the occurrence of gastric ulcers and to set up an institutional mechanism for animal welfare.

This is the first study to investigate the prevalence of gastric ulcers in Thoroughbred racehorses after horse racing in Korea. This work compares the prevalence and severity of gastric ulcers in the non-glandular region (NG) and in the pyloric region (P). The drug efficacy of ranitidine, which is the most prevalent treatment option, and omeprazole, which is newly introduced, is compared in racehorses that have undergone intense training and are actively participating in races.

MATERIALS AND METHODS

Horse recruitment and gastroscopic examination

Forty-nine Thoroughbred racehorses (11 stallions, 9 geldings and 29 fillies) in active race training aged 2–8 years with a body weight from 405 to 509 kg were randomly recruited through a recruitment announcement on a first-come, first-served basis. These horses were considered either to be healthy or to have clinical signs of gastric ulcers by the trainer. Although some horses had clinical symptoms related to gastric ulcer, such as anorexia and mild weight loss, physical examination showed no abnormal findings. Recruited horses were scheduled to undergo gastroscopy within two days after racing. In preparation for gastroscopy, the horses were fasted for 12–18 hours prior to gastroscopy, and water was withheld for four hours.

After the measurement of body weight, all horses were sedated with intravenous detomidine (Equadin; Dong bang, Korea) at 20 μ g/kg and examined for the presence of gastric ulcers using a 13-mm-diameter, 3.25 m flexible videoendoscope (KARL STORZ endoscope; Karl Storz, Germany). It was essential to examine the entire stomach, including the cardia, margo plicatus, greater curvature, lesser curvature, pyloric antrum, and the proximal duodenum (if desired) [13].

Grading

Both the NG and P of the stomach were evaluated by three veterinarians who did not engage in discussions with each other. A standard grading system with scales ranging from 0 to 4 was used to grade the severity of the ulcers [14,15]. According to this grading system, grade 0 = the epithelium is intact, and there is no appearance of hyperaemia or hyperkeratosis, grade 1 = the mucosa is intact, but there are areas of hyperaemia or hyperkeratosis, grade 2 = small, single, or multifocal (< 5) lesions, grade 3 = large, single, or multifocal (\ge 5) lesions or extensive superficial lesions, and grade 4 = extensive lesions with areas of apparent deep ulceration.

The grades from the three veterinarians were summed, turned into a sum grade (SG), and it was represented through 0–12 grades (a total of 13 grades). The SG was divided into five stages: SG 0 = normal, SG 1–3 = minimal, SG 4–6 = mild, SG 7–9 = moderate, and SG 10–12 = severe.



Treatment

After agreement of treatment by the trainer and/or the owner, horses with mild or more gastric ulcer among the 49 horses were selected as the treatment group, and the lowest grade in the selected treatment group was 5. At the time of the experiment, ranitidine (Ranitidine HCl Tab. 150 mg Nelson; Nelson Pharm Korea, Korea) and omeprazole (AbGard; Abler Pharmaceuticals, USA) were both banned from horse racing in Korea, so horses in competition within 10 days of treatment could not participate in the experiment. To reduce the number of experimental errors, 12 racehorses in race training were selected and randomly assigned to the ranitidine- or omeprazole-treated groups. Seven horses had been treated with ranitidine and another five with omeprazole. The ranitidine dosage for horses was 6.6 mg/kg administered orally three times per day for 28 days, and 4.0 mg/kg of omeprazole was orally administered once a day for 28 days.

Follow-up evaluation and statistical analyses

Follow-up gastroscopy was scheduled for within one to five days after finishing 28 days of treatment. Variations in the timing of the repeated gastroscopy were allowed to accommodate the horses' racing schedule. Sedation, restraint, and the technique of gastroscopy were the same as in the previous examination. One horse from the omeprazole-treated group was lost to follow-up because the horse had lameness and its race schedule was canceled by the trainer.

A free software environment (R for Windows 4.1.0; R Core Team [2021], Austria) for statistical computing and graphics was used for data analysis. The ulcer grade of the NG and the P of all the enrolled horses was compared using a paired t-test. Pearson's correlation coefficients were used for the correlation analysis. To compare the gastric ulcer grades before and after treatment, the Shapiro-Wilk test was performed, and if the preliminary test for normality was not significant, the paired t-test was used; if the preliminary test rejected the null hypothesis of normality, a non-parametric test (Wilcoxon's signed-ranks test) was applied in the main analysis. A Mann-Whitney U test was performed to compare the efficacy of ranitidine and omeprazole. The results are presented as mean \pm SD, and significance was determined when p < 0.05.

RESULTS

Prevalence and regional distribution

The prevalence and regional distribution of the gastric ulcers in Thoroughbred racehorses in Korea are shown in **Table 1**. All horses examined in this study had gastric ulcers with a score of at least SG 1 and above, and the severity of ulcers was higher in the NG than in the P; the moderate stage showed the highest ratio (47%) in the NG, but in the P, minimal and mild

Table 1. The prevalence and the regional distribution of the ulcers according to their sum grade

SG	NG	Р
0 (normal)	0 (0)	0 (0)
1–3 (minimal)	6 (12)	20 (41)
4-6 (mild)	13 (27)	20 (41)
7-9 (moderate)	23 (47)	8 (16)
10-12 (severe)	7 (14)	1 (2)
Sum	49 (100)	49 (100)

Values are presented as number (%).

SG, sum grade; NG, non-glandular region; P, pyloric region.



Table 2. The mean sum grade before and after treatment in both NG and P of horses

Groups	Before treatment	After treatment	p value
RT28 NG	$8.7 \pm 2.4 (n = 7)$	$3.9 \pm 1.2 (n = 7)$	< 0.001*
RT28 P	$3.3 \pm 2.6 (n = 7)$	$2.4 \pm 1.0 (n = 7)$	0.231
RT28	$6.0 \pm 3.7 (n = 14)$	$3.1 \pm 1.3 (n = 14)$	0.003 [†]
OT28 NG	$8.3 \pm 3.0 (n = 4)$	$0.8 \pm 1.0 (n = 4)$	0.003 [†]
OT28 P	$7.8 \pm 1.3 (n = 4)$	$1.0 \pm 0.8 (n = 4)$	< 0.001*
OT28	$8.0 \pm 2.1 (n = 8)$	$0.9 \pm 0.8 (n = 8)$	< 0.001*

NG, non-glandular region; P, pyloric region; RT28, 28th day reassessment after administration of ranitidine 6.6 mg/kg PO, t.i.d.; OT28, 28th day reassessment after administration of omeprazole 4.0 mg/kg PO, s.i.d. $^*p < 0.001$; $^\dagger p < 0.01$.

Table 3. The difference of variation of the mean sum grade in the ranitidine administration group and the omeprazole administration group

Anatomic region	vRT28	vOT28	p value
NG	$-4.9 \pm 2.3 (n = 7)$	$-7.5 \pm 2.1 (n = 4)$	0.039*
Р	$-0.9 \pm 2.2 (n = 7)$	$-6.8 \pm 0.5 (n = 4)$	0.005 [†]

NG, non-glandular region; P, pyloric region; vRT28, the difference of variation of the mean sum grade in RT28; vOT28, the difference of variation of the mean sum grade in OT28.

*p < 0.05; †p < 0.01.

stage showed the highest ratio of 41%, respectively. Only 2% of horses had severe gastric ulcers in the P as compared to 14% of the horses that had severe gastric ulcers in the NG. The mean SG (mSG) of the 49 enrolled horses was significantly higher in the NG than in the P at 7.2 ± 2.5 and 4.5 ± 2.6 , respectively (p < 0.001). As a result of the correlation analysis of the mSG of the NG and P, the Pearson product-moment correlation coefficient was -0.16 (p = 0.26), indicating that there was no correlation between the two variables.

Efficacy of ranitidine and omeprazole

The mSG of pre- and post-treatment is shown in **Table 2**. In the ranitidine-treated group, the mSG significantly decreased in the NG (from 8.7 ± 2.4 to 3.9 ± 1.2 , p < 0.001). The mSG of P also decreased, but this effect was not significant (from 3.3 ± 2.6 to 2.4 ± 1.0 , p = 0.231). In the omeprazole-treated group, the mSG significantly decreased in both NG (from 8.3 ± 3.0 to 0.8 ± 1.0 , p = 0.003) and P (from 7.8 ± 1.3 to 1.0 ± 0.8 , p < 0.001).

Table 3 shows the results of comparing the efficacy of ranitidine and omeprazole. The difference in the variation of mSG before and after treatment was greater in the omeprazole-treated group (vOT28) compared to the ranitidine-treated group (vRT28). According to the results of the Mann–Whitney U test, the therapeutic effect of omeprazole was better than ranitidine in both NG (p = 0.039) and P (p = 0.005).

Endoscopic images and mSG before and after treatment are shown in **Fig. 1**. In the ranitidine treatment group, a mSG of 12 before treatment improved to a mSG of 5 after treatment in the NG, and a mSG of 8 before treatment improved to a mSG of 3 after treatment in the P. In the omeprazole treatment group, a mSG of 12 before treatment improved to a mSG of 2 after treatment in the NG, and a mSG of 8 before treatment improved to a mSG of 1 after treatment in the P.

DISCUSSION

Gastric ulcers are very prevalent and have an extremely significant economic and clinical impact on racehorses; however, it is impossible to make a definitive diagnosis before

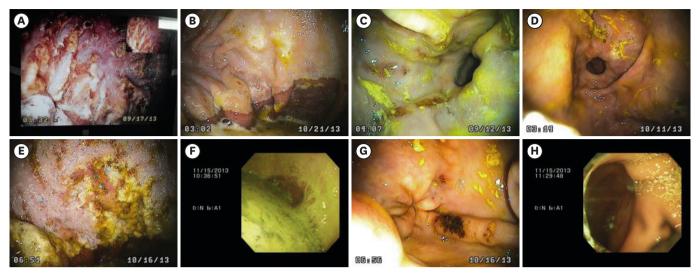


Fig. 1. Endoscopic images and mSG before and after treatment. (A) NG before treatment in the ranitidine treatment group (mSG = 12). (B) NG after 28 days of ranitidine treatment in the ranitidine treatment group (mSG = 8). (C) P before treatment in the ranitidine treatment group (mSG = 8). (D) P after 28 days of ranitidine treatment in the ranitidine treatment group (mSG = 3). (E) NG before treatment in the omeprazole treatment group (mSG = 12). (F) NG after 28 days of omeprazole treatment in the omeprazole treatment group (mSG = 8). (H) P after 28 days of omeprazole treatment in the omeprazole treatment group (mSG = 8). (H) P after 28 days of omeprazole treatment in the omeprazole treatment group (mSG = 1). mSG, mean sum grade; NG, non-glandular region; P, pyloric region.

confirming a finding through gastroscopy, so the importance of treating gastric ulcers has been overlooked. According to previous studies, the prevalence of gastric ulcers in Thoroughbred racehorses in race training was reported to be 91% and increased to 100% in actively racing horses [16]. Additionally, the prevalence of gastric ulcers is different depending on the purpose of the horse. The prevalence of gastric ulcers is higher in racehorses as compared to non-racing horses, and there is a positive correlation between the occurrence of gastric ulcers and the intensity of training among racehorses [16-18]. However, in the Korean Thoroughbred racehorses examined in this study, the prevalence of gastric ulcers after the race was revealed to be 100%, although the average starts per year per horse in Korea (5.74 times) was less than that of Hong Kong or Japan (by more than seven times) according to the 2018 annual report of the International Federation of Horseracing Authorities (IFHA) [19]. Because the importance of gastric ulcers in racehorses has been overlooked in Korea, the therapeutic and preventive agents, such as ranitidine or omeprazole, were not allowed to be prescribed within 10 days before races. It can be assumed that the exposure to the risk of gastric ulcers during the two weeks before the race in which the intensity of training is highest can be attributed to this high prevalence. The results of this study reflect how significant gastric ulcers are in Korean racehorses.

Begg and O'Sullivan [5] commented that the prevalence of gastric ulcers in the NG and P are remarkably different (p < 0.05), and once the gastric ulcer happens, the grade of the pyloric ulceration appears to be remarkably lower than that of the NG ulceration. Unlike previous study [5], the prevalence of gastric ulcers in racehorses participating in this study was confirmed to be 100% in both NG and P. As for the severity of gastric ulcers, as in previous study [5], the grade of gastric ulcers in the NG (7.2 ± 2.5) was significantly higher than that in the P (4.5 ± 2.6) (p < 0.001). Recently, equine gastric ulcer syndrome (EGUS) was studied by subdividing it into equine squamous gastric disease (ESGD) and equine glandular gastric disease (EGGD). Banse and Andrews [20] suggested that the pathophysiology of EGGD has not yet been clearly identified, and the relationship between the presence or severity of



ESGD and that of EGGD is inconsistent, so the two types of gastric ulcers require different treatments or management strategies. Gastric ulcers in ESGD and EGGD differ in terms of causative mechanisms. ESGD occurs due to prolonged exposure to acids and pepsin caused by phenomena such as gastroesophageal reflux disease syndrome in humans. In racehorses, non-glandular ulcers are often the result of increased abdominal pressure and decreased stomach volume during training [4], and exercise may inhibit gastric emptying, which causes prolonged exposure of the NG to gastric juice. The glandular region contains glands that secrete mucosal protective factors (bicarbonate, mucus) and mucosal aggressive factors (hydrochloric acid, pepsin). Therefore, pyloric ulcers are caused by blood flow disturbances and decreased bicarbonate and mucus secretion, which results in damage to the submucosa [21]. Based on the results of this study, the prevalence of gastric ulcers after the racing of Korean Thoroughbred racehorses was confirmed to be 100% in the NG and in the P, and judging that the mSGs in the two regions are not related to each other, it can be assumed that ESGD and EGGD occur by different mechanisms, and that certain factors related to horse racing training or horse racing itself may also affect P ulcers. Further research should be conducted to determine the association between various disciplines and EGGD and to determine the mechanisms behind ESGD and EGGD, which will lead to the study of suitable gastric ulcer treatments for ESGD and EGGD, respectively, in racehorses.

Omeprazole is widely used in the treatment and prevention of EGUS. Studies of gastric ulcer treatments and the preventative efficacy of omeprazole in horses have actively been conducted [22-24], and most studies have used only FDA-approved GastroGard (Boehringer-Ingelheim, Germany) as the medicine for equine gastric ulceration among omeprazole formulations. Furthermore, its efficacy has already been demonstrated [9,25]. However, ranitidine, which has been used as a therapeutic agent for equine gastric ulcers in Korea, was compared to AbGard of Abler in this study. AbGard was chosen because Sykes et al. [26-28] previously demonstrated it to be effective in treating NG ulcers, and with an acceptable price, as it is about half that of GastroGard. Through this study, it was confirmed that both ranitidine and omeprazole had a significant improvement or treatment effect on gastric ulcers in the NG, but only omeprazole had a significant improvement and treatment effect on gastric ulcers in the P (**Table 2**).

Lester et al. [9] found that omeprazole is more effective than ranitidine in healing gastric squamous ulcers in Thoroughbreds in race training. In three recent studies, only 25% of glandular ulcers healed with 28–35 days of omeprazole therapy at 4.0 mg/kg orally once a day in direct contrast to a squamous healing rate of 78% [26-28]. Furthermore, adjunctive treatments such as antimicrobials should be considered rather than omeprazole monotherapy for the treatment of glandular-region ulcers. In this study, omeprazole showed a significantly better therapeutic effect than ranitidine in the P and in the NG (**Table 3**). In all four horses treated with omeprazole, the grade of gastric ulcer was significantly reduced in both the NG and the P, confirming that omeprazole monotherapy was sufficiently effective in treating pyloric gastric ulcer. The reason for showing different results from previous studies [26-28] may be found in the differences in the Korean horses' racing environments, diet, and overall management, so additional research is needed to determine why omeprazole has good therapeutic effects in both NG and P in Korean racehorses.

As previously mentioned, gastric ulcers in racehorses were not considered to be important in Korea until this study was conducted. Additionally, omeprazole paste was not commercially available. Drugs such as ranitidine and omeprazole were included in the doping test list for racehorses, so horses exposed to a high risk of gastric ulcers due to intensive race



training were not receiving these drugs within 10 days of a race. However, the importance of diagnosing and treating gastric ulcers has been revealed based on the results of this study, and the number of requests for gastroscopy is increasing. Additionally, the use of AbGard, which was more effective than ranitidine in both NG and P, has become possible in Korea with the permission of the Ministry of Food and Drug Safety (MFDS). As a result, the use of omeprazole is now allowed until the day before a race, as omeprazole has been excluded from the list of prohibited drugs in racehorses.

Omeprazole paste will be useful for the treatment and prevention of gastric ulcers in Korean Thoroughbred racehorses who suffer gastric ulcers at a rate of 100%. This is one of the biggest changes for the welfare of racehorses in Korea in recent years, and additional studies on the improvement of athletic performance in Korean racehorses after the use of omeprazole should be conducted. In addition, although no adverse side effects are listed in the manufacturer's provided information, racehorses will continue to receive prophylactic doses after 28 days of treatment, so studies on the side effects of chronic acid suppression therapy are needed to help reduce unnecessary side effects and costs and improve quality of care.

This study had several limitations. One of the limitations of this study was the small sample size. At the time of this study, ome prazole was prohibited drug for racehorses and it is required withdrawal period of 10 days to compete in the race. It was difficult to get many horses to participate in the experiment because of the burden of the withdrawal period because most horses participated in the race without rest. But now, omeprazole can be allowed up to one day before the race in Korea, it will be easier to enroll more horses in subsequent studies, which will lead to more meaningful results. Another limitation of this study was the inability to control other factors that could induce gastric ulcer during the study period. As it has already been revealed, gastric ulcers in horses are caused by a variety of factors including diet and feeding management, stress of training or disease, stress of social environment, mechanics of training as well as long term use of medications such as non-steroidal anti-inflammatory drugs. In particular, in the case of racehorses, it is a high possibility that various factors may have had a complex effect on gastric ulcers. Since the study was not conducted on experimental horses, but on horses participating in actual races, it was not possible to control various factors uniformly. However, in order to obtain as accurate data as possible, the horses immediately after the race at the same racecourse were selected for the experiment.

This study confirmed that Thoroughbred racehorses after racing had 100% gastric ulcers and that omeprazole is more effective than ranitidine for the treatment of ESGD and EGGD in racehorses actively participating in races. In addition, the prohibited substances clause of the Horse Racing Regulations has been changed to allow racehorses to receive omeprazole prophylactically during the racing training period, which is when horses have the highest risk of gastric ulcers. As a result, information on gastric ulcers in racehorses was provided to horse racing officials, and they changed their perceptions regarding the treatment and prevention of gastric ulcers, contributing to the improvement of the welfare of racehorses in Korea.

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