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Short communication

ANTIMICROBIAL PROPHYLAXIS IN ADDITION TO PREMEDICATION IN GASTROINTESTINAL SURGERY

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The aim of this study was to evaluate three combinations of antibiotics applied perorally prior to laparotomy and gastrointestinal surgery and to select the most favorable combination. Research was performed on 24 female and male dogs divided into four groups. Following abdominal wall incision the caecum was compressed manually and 5 mL of saline solution was injected into it. Five mL of caecum contents was aspirated in a sterile syringe and only 0.1 mL was incubated into blood agar and homogenous agar. Bacterial colonies were counted and determined. Prior to surgery the control group (n=6) received no antibiotics. The group which received the combination of gentamicin and clindamycin (n=6) achieved the best reduction of *E. coli* whereas *Enterococcus faecals* was 100% destroyed. The group which received amoxicillin with clavulanic acid and metronidazole (n=6) acquired a reduction of bacteria *Enterococcus faecalis*, which could be sufficient for prophylaxis. The combination of gentamicin and erythromycin (n=6) failed to accomplish a reduction of the number of bacteria.

Key words: antibiotics, intestinal micro flora, microbiology analysis

INTRODUCTION

Microbes play a crucial role in the host health. They serve as a defending barrier against invading pathogens, aid in digestion and energy collection from the diet, assist in nutritional entrance into enterocytes and stimulate the local immune system [1].

Gastrointestinal surgery procedures due to its anatomical and physiological attributes is demanding. Thus, prevention of complications caused by contamination of the abdominal cavity with microorganisms that are naturally present in the gastrointestinal (GI) system [2] or intraperitoneal leakage of bacteria from gastrointestinal system [3] is essential.

Septic peritonitis is a potentially life- threatening condition with a mortality rate of about 50%. Septic peritonitis may be caused by intestinal perforation due to foreign

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body, administration of non-steroidal anti-inflammatory drugs, neoplasia or dehiscence of the previous surgical site [4]. Lanz et al [5] reported that in 75% of septic peritonitis is caused by perforation of the gastrointestinal tract. Furthermore, peritonitis can be caused by *Candida* spp. in immune-compromised animals because *Candida* spp. is an opportunistic pathogen [6].

The aim of intravenous applications of antibiotics prior to surgery procedures is to reach a sufficient concentration in the tissues that are exposed to possible contamination with the liquid content originated from the gastrointestinal system.

The advantage of oral application of antibiotics such as gentamicin is in the lack of systemic resorption and subsequent reduction of bacteria in the ileum, caecum and colon which are the bacteria richest parts of the gastrointestinal system [7].

During selection of prophylactic antibiotics the following should be taken into consideration: source of contamination, proven efficacy against the potentially contaminating microorganisms, systemic toxicity of selected antibiotics, cost, possible side effects and pharmacokinetic properties [8].

Bacteria which penetrate in the surgery field can be destroyed by systemic application of antibiotics within 3 hours from the beginning of the infection; it means that antibiotics should be present in the tissue before surgery. If a long time period elapsed from the moment of infection to the moment of the application of antibiotics and its penetration into the tissue the effect is lower. In the human abdominal surgery, it is advisable to apply antibiotics 48 hours prior to the surgery [9]. In small animal surgery, postoperative peritoneal infection is often caused by *Escherichia coli*, *Staphylococcus aureus* and *Pasteurella* spp. [8].

It is essential to use narrow spectrum antimicrobials in order to reduce target microorganisms during gastrointestinal surgical procedures. Application of wide spectrum antibiotics can lead to an increased risk of side effects like super infection, increased number of resistant bacteria, and bacterial dysbiosis. It is also important that long-term administration of antimicrobials is restricted whenever is possible in order to avid unwilling side effects [10-12]. Coagulase positive *Staphylococcus aureus*, *Enterococcus spp.* and *Escherichia coli* are aerobes which often cause peritonitis [13]. The distal part in comparison to the proximal part of gastrointestinal system like the ileum, colon and rectum contain more of the above mentioned bacteria. The selection of antimicrobials should be based on the anatomical part of the gastrointestinal system involved in the surgical procedure. The first generation of cephalosporins should be applied prior to surgery on the upper and middle part of the small intestine, whereas the second generation is prefered for the distal part of the small intestine and large intestine. Re-application of antibiotics should be done within 2 to 10 hours [14]. Only oral applications of antibiotics reduce and/or destroy pathogenic bacteria in the gastrointestinal system, and even if stomach and gut content leakage and pour into the peritoneal cavity has occurred, there is no risk of peritonitis.

The aim of this study was to evaluate three combinations of antibiotics applied perorally prior to laparotomy and gastrointestinal surgery and to select the most favorable combination.

MATERIALS AND METHODS

In 24 dogs, who were patients at the Veterinary Practice Koprivnica, during surgical abdominal cavity aspiration of the caecum was performed in order to determine bacteria. Dogs were divided into four groups; in each group were 6 dogs (3 males and 3 females). Owners of the dogs who were included in this research signed the formal consent. The ethical committee, Faculty of Veterinary Medicine Zagreb and Ministry of Agriculture, Republic of Croatia also approved this study. All dogs were in general anesthesia provided by diazepam (Apaurin® Pliva, Croatia) and ketamine (Ketaminol® Vetaquinol, Switzerland) applied intravenously. Analgesia was maintained prior to, during and following surgery with karprofen (Norocarp® Norbrook, USA). ASA (American Society of Anesthesiologists) assessed the physical status of the patient who underwent to surgery procedure (in the current research- laparotomy). All doges were assessed as ASA 1, ASA 2, or ASA 3 in correlation to their physical condition. Indications for laparotomy were ileus, impaction of caecum content, obstruction of pylorus, linear foreign body, chronic intestinal obstipation, ovariohysterectomy, pyometra and urolith extraction. Following abdominal wall incision the caecum was compressed manually and 5 mL of saline solution was injected into the cecum. Five mL of caecum contents was aspirated in a sterile syringe and only 0.1 mL was incubated into blood and homogenous agar. Pots were incubated in aerobic and anaerobic conditions at 35ºC for 48 hours. Following incubation bacterial colonies were counted and determined. When samples were received in the laboratory, Gram staining was performed in purpose for polymorphonuclear leukocyte counting. In the current research there were four groups, in each group were six dogs (3 males and 3 females); altogether 24 dogs. The first group (n=6) was the control group and antimicrobial prophylaxis prior to surgery was omitted. The second group (n=6) perorally received gentamicin (Gentamicin® Pliva, Zagreb, Croatia) a dose of 8 mg/kg and erythromycin (Erythromycin® Belupo, Koprivnica, Croatia) in a dose of 8 mg/kg 24 and 12 hours prior to surgery. The third group (n=6) perorally received gentamicin in a dose of 8 mg/kg (Gentamicin® Pliva, Zagreb, Croatia) and clindamycin in a dose of 10 mg/kg (Klimicin®, Lek, Ljubljana, Slovenia). The fourth group (n=6) received metronidazole (Medazol®, Belupo, Koprivnica, Croatia) in a dose of 20 mg/kg and amoxicillin and clavulanic acid (Amoxiclav®, Lek, Ljubljana, Slovenia) in a dose of 20 mg/kg.

RESULTS AND DISCUSSION

Table 1. contains data on breed, average age, gender and surgery procedure of all dogs included in the investigation. The youngest dog was 8 months old and the oldest one was 96 months old.

In all observed samples (n=6) in the control *Escherichia coli* 10^3-10^5 per 100 μl and *Enterococcus faecalis* 10^3-10^5 per 100 μl were isolated.

In the group treated with gentamicin and erythromycin, following bacteria were isolated:

- *Escherichia coli* in 66% (4/6) of samples in total number 10^5 per 100 μl
- *Pantoea* spp. in 16.6% (1/6) of samples in total number 10^5 per 100 μl

- *Serratia marscencens* in 16.6% (1/6) of samples in total number 10^5 per 100 μl
- *Klebsiella* spp. in 16.6% (1/6) of samples in total number 10^5 per 100 μl
- *Strenotrophomonas maltophilia* u 16.6% (1/6) of samples in total number 10^5 per 100 μl

In the group treated with gentamicin and clindamycin the following bacteria were isolated:
- *Escherichia coli* in 100% (6/6) of samples in total number 10^4-10^5 per 100 μl
- *Klebsiella* spp. in 33.3% (2/6) of samples in total number 10^3-10^5 per 100 μl
- *Enteroccocus faecalis* in 100% (6/6) of samples in total number 10^4-10^5 per 100 μl
- *Proteus* spp. in 33.3% (2/6) of samples in total number 10^3-10^5 per 100 μl

Table 1. Data regarding breed, average age, gender and surgery procedure of all dogs included in the investigation

Breed	Age (months)	Gender	Surgery	*Groups
German Shepherd	36	male	foreign body in jejunum	A
Hungarian Vizsla	18	female	ovariohyterectomy	A
Sarplaninac	24	male	gut resection	A
Mixed	36	male	urine bladder rupture and multiple perforation of small intestine	A
Doberman	72	female	ovariohysterectomy	A
Cocker Spaniel	36	female	ovariohysterectomy	A
Samoyed	60	female	pyometra	B
Labrador	72	female	pyometra	B
Irish Setter	96	male	neoplasia jejunum	B
Dalmatian	24	male	ventral hernia	B
Mastiff	60	female	pyometra	B
Mixed	48	male	foreign body in jejunum	B
German Boxer	11	male	enterotomy	C
Alaskan Malamute	48	male	gastrotomy	C
Cocker Spaniel	42	female	colonotomy	C
Stafford Terrier	60	female	pyometra	C
Basset Hound	8	male	foreign body in jejunum	C
Mixed	96	female	pyometra	C
Stafford Terrier	18	male	foreign body in jejunum	D
Dalmatian	48	female	ovariohysterectomy	D
German Springer	24	female	tiflectomy	D
German Springer	60	female	pyometra	D
Mixed	96	male	tiflectomy	D
German Boxer	36	male	urolithiasis	D

*group A = control group (n=6); group B = group treated with erithromycin and gentamicin (n=6); group C = group treated with clindamycin and gentamicin (n=6); group D = group treated with amoxicillin/clavulanic acid and metronidazole (n=6)

In the group treated with amoxicillin/clavulanic acid and metronidazole the following bacteria were isolated:
- *Esherichia coli* in 83.3% (5/6) of samples in total number 10^5 per 100 μl
- *Pantoea* spp. in 16.6% (1/6) of samples in total number 10^5 per 100 μl
- *Enterococcus faecalis* in 50% (3/6) of samples in total number 10^4-10^5 per 100 μl.

The aim of this study was to evaluate three combinations of antibiotics applied perorally prior to laparotomy and gastrointestinal surgery and to select the most favorable one.
Hemorrhage and bacterial contamination with bowel content are the major post surgical complications in the gastrointestinal system [15,16]. Two bacteria *Escherichia coli* and *Clostridium* spp. are the main producers of bacterial toxins and also, very toxic are *Enterococcus faecalis* and *Staphylococcus aureus* [17].
As shown in the results in all tested samples, including the control, group *Clostridium* spp. was isolated whereas, according to Culp et al. [3] *Clostridium* spp. was isolated in 3 cases out of 24 if primary peritonitis occurred. It seems that *Clostridium* spp. is a very rare cause of primary peritonitis (12.5%) and if prophylactic antibiotics were applied prior to surgery secondary peritonitis failed to occur. *Clostridium* spp. is often found in the caudal portion of the gastrointestinal system; in the large intestine which is considered normal, the expectance of pathological changes during long lasting absence of peristalsis, thus bacteria from the caudal part can migrate into the cranial part of the intestine. In the control group *E. coli* was isolated from each sample (n=6), however in the previous study conducted by Culp et al. [3]. *E. coli* was isolated only in 3 cases out of 9. Duration of antibiotics application in prophylactic purposes should be minimal but effective. In the current research antibiotics were applied twice (24 and 12 hours) prior to surgery in the form of tablets and cream applied perorally. The antimicrobial substance has to achieve an efficient concentration minimally 24 hours prior to surgery in order to provide reduction of bacteria [8].
The obtained results reveal that the group treated with clindamycin in doses of 10 mg/kg and gentamycin in doses of 8 mg/kg applied orally eliminate *Enterococcus* spp. whereas *Enterococcus* spp. and *E. coli* were isolated in all sample taken from the control group. Both bacteria are the most often potential cause of post surgical infection following surgical procedures in the intestine. It was evident that lack of *Enterococcus* spp. enhances *Serratia marscencens* and *Strenotrephomonas maltophilia* allowed life space in the intestine and their multiplication and spreading, in fact bacterial dysbiosis was detected [18]. That fact was also supported by the control group where only *E. coli* and *Enterococcus faecalis* were isolated.
Prior to surgery, application of amoxicillin with clavulanic acid in doses of 20 mg/kg and metronidazole in doses of 20 mg/kg perorally obtained partial results in elimination of *Enterococcus* spp. from the caecum because only one sample was free of *E. coli* and *Enterococcus faecalis*. The above mentioned combination of antibiotics accomplished partial reduction of pathogenic bacteria, which could be sufficient for prophylaxis.
In this prophylactic procedure, as a consequence of reduction in pathogenic microflora nonspecific and nontoxic microorganisms such as *Pantoea* spp. were isolated from the caecum.

The combination of erythromycin and gentamicin applied perorally both in doses of 8 mg/kg minimally reduced bacteria in the ileocecal part of the intestine. Opposed results were obtained with neomycin which is also an aminoglycoside as gentamicin and erythromycin which are considered the most effective [8]. Holle et al. [19] in their investigation reported that erythromycin increases intestinal motility and therefore reduces bacteria because normal intestinal motility is a major defense mechanism against the attachment of pathogenic bacteria in the small intestine [1]. In the current research in intestinal dysbiosis occurred, owing to that, *Klebsiella* spp. and *Proteus* spp. were dominant in the isolated material.

In conclusion, the group which received the combination of gentamicin and clindamycin achieved the best reduction of *E. coli* whereas *Enterococcus faecals* was 100% destroyed. The group which received amoxicillin with clavulanic acid and metronidazole acquired a significant reduction of bacteria *Enterococcus faecalis*, which was sufficient for prophylaxis. The ombination of gentamicin and erythromycin failed to accomplish sufficient reduction of bacteria.

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ANTIMIKROBNA PREMEDIKACIJA KAO PROFILAKSA PRI IZVOĐENJU HIRURŠKIH ZAHVATA U ABDOMENU

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Cilj ovog istraživanja bio je da se procene tri kombinacije antibiotika primenjenih peroralno pre laparotomije i gastrointestinalne hirurgije i da se odredi najefikasnija kombinacija. Istraživanje na psima je izvedeno na 24 mužjaka i ženke podeljene u četiri grupe. Nakon incizije abdominalnog zida slepo crevo je pritisnuto i ubrizgano je 5 mL fiziološkog rastvora u njega. Pet mL sadržaja slepog creva je aspirirano u sterilne injekcione špriceve, od čega je samo 0,1 mL inkubiran na krvni i homogeni agar. Nakon toga su prebrojane i determinisane bakterijske kolonije. Pre hirurškog zahvata kontrolna grupa (n=6) nije primila antibiotik. U grupi koja je primila kombinaciju gentamicina i klindamicina (n=6) ostvareno je najveće smanjenje broja *E. coli*, dok je *Enterococcus faecalis* uništen u 100% efektu. U grupi koja je primila amoksicilin - klavulansku kiselinu i metronidazol (n=6) ostvareno je smanjenje broja bakterije *Enterococcus faecalis*, što bi moglo da bude dovoljno za profilaksu. Kombinacija gentamicina i eritromicina (n=6) nije ostvarila zadovoljavajuće rezultate.