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   Mohammed A. Nasreldin
Whether to use or Not Prophylactic Antibiotics in Automated Peritoneal Dialysis Patients Undergoing Colonoscopy, A Prospective Controlled Randomized Study

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Abstract

The aim of our study was to look at the overall risk of peritonitis post colonoscopy in end stage renal disease patients on automated peritoneal dialysis and to evaluate the use of prophylactic antibiotic in those patients when given prior to colonoscopy.

A total of 93 patients out of 134 patients on automated peritoneal dialysis (APD) undergoing diagnostic colonoscopy were enrolled in a prospective randomized study. The study extended from January 2016 throughout May 2018. Patients were randomized into two age and sex matched groups; group 1 (46 patients) who had prophylaxis cefazidime prior to colonoscopy and group 2 (47 patients) who had colonoscopy without prophylactic antibiotics. The following parameters: age, gender, duration on dialysis, duration on APD, diabetic status, use of antibiotics before the procedure, and indications for and findings of colonoscopy were studied. Prophylactic antibiotics were given for prevention of peritonitis if needed according to the 2010 ISPD guidelines.

Results: Post-colonoscopy peritonitis was documented in 2 (4.3%) and 3 (6.4%) patients in groups A and B respectively (p > 0.05). The most common causative agents were gram negative bacteria and there were no other complications.

Conclusion: There was no strong correlation between prophylactic antibiotic use and risk of peritonitis in peritoneal dialysis patients and it seems that the overall risk of developing peritonitis after colonoscopy is low. Only old age, diabetes mellitus and low serum albumin appear to be of significance. Polypectomy; partial or complete did not increase peritonitis episodes in our study population.

Keywords: APD, ESRD, diabetes, colonoscopy, polypectomy, antibiotic prophylaxis, peritonitis.

Introduction

Peritonitis is a well-recognized complication of peritoneal dialysis. The most common causes of peritonitis are probably skin contamination and peritoneal catheter infections. However, the colon is also felt to be a potential source of dialysate contamination, especially in patients who have diverticulitis (1). The incidence of colonoscopy-induced bacteremia is variable, reported from 0% to 27% of patients (2, 3). It has been suggested that antibiotic prophylaxis be given to immunocompromised patients and those with known valvular heart disease or prostheses prior to colonoscopy (4, 5). Few cases have been reported in the literature on peritonitis following colonoscopy in CAPD patients (6-10). These reports suggested that diagnostic instrumental procedures such as colonoscopy may precipitate gram-negative peritonitis in CAPD patients. Due to improvements in peritoneal dialysis technique and the enforcement of the aseptic precautions, there has been a reduction in peritonitis caused by gram-positive but not gram-negative organisms (11). The few case reports in the literature on peritonitis following colonoscopy were all in CAPD but not on APD patients (6, 7, 12-15). In the 2007 series reported by Yip et al (11), 3 of 5 peritonitis episodes were culture negative. The authors could not explain the cause of such a high percentage of culture negative results. The organisms causing these 3 episodes of peritonitis might not have originated from the gastrointestinal tract. In the same series, the risk of developing CAPD peritonitis after colonoscopy in patients without antibiotic prophylaxis was statistically not significant. The 2016 International Society for Peritoneal Dialysis (16) Guidelines showed evidence 2-C favoring the use of prophylaxis antibiotics prior to the procedure (16). However, there has been little literature to support this recommendation. The objective of the present study was to investigate the risks and outcomes of peritonitis after flexible colonoscopy and to show whether there
is a need for prophylactic antibiotics in automated peritoneal dialysis (APD) patients undergoing this procedure.

**Patients and methods**

Between January 2016 throughout May 2018, 93 patients, (68 males, 25 females) were included in this study. Patients were randomized (1:1) into two groups; Group A: 46 patients on APD with prophylactic antibiotic therapy before the flexible colonoscopy, Group B: 47 patients on APD without prophylactic antibiotics (Table-1). Exclusion criteria were: history of colonic or rectal resection, neurologic deficit, pregnancy, ongoing sepsis, valvular or chronic heart disease, urinary tract infections, chronic liver disease, exit-site or tunnel infections, pneumonia or pulmonary tuberculosis, peritonitis or history of peritonitis for the last one year and unwillingness to give informed consent (Figure-1). All flexible colonoscopy examinations were performed by trained gastroenterology consultants. All Staff in the endoscopy unit were aware of the potential hazard of cross-infection and assiduous mechanical cleaning followed by disinfection was done. The following parameters: age, gender, duration on dialysis, diabetic state, use of antibiotics before the procedure, and indications for and findings of colonoscopy were studied. APD peritonitis episodes occurring within 1 week after colonoscopy, culture results and outcomes of peritonitis were recorded. At our center, the colonoscopy bowel preparation protocol included a low residue diet 2 days before the examination and patients are instructed to take a fluid diet the day before the procedure. Oral electrolyte lavage solutions or aqueous sodium phosphate solution were used as laxative for bowel preparation. Peritoneal dialysis effluent (PDE) was drained and the patient’s abdomen was kept empty before the procedure. Prophylactic antibiotics were given for prevention of peritonitis if needed according to the 2010 ISPD guidelines (17). Prophylactic antibiotics for APD peritonitis prevention were not routine at our center. Peritonitis was diagnosed when abdominal pain and cloudy fluid occurred with or without fever, and when peritoneal fluid white blood cell (WBC) count was ≥100/mm3, with >50% neutrophils. Episodes with peritoneal eosinophilia but negative bacterial culture were excluded. The PDE was sent for hematological and microbiological examination when patients complained of abdominal pain or if the PDE was turbid. For the microbiological tests, 50 mL peritoneal fluid was centrifuged at 5000g for 15 minutes. The deposit was inoculated on 5% sheep blood agar, MacConkey agar, and Sabouraud agar and incubated aerobically at 35°C for up to 72 hours. All isolates were identified by standard biochemical methods and the identity of the isolates was confirmed using the Vitek Automicrobial System (bioMerieux, Vitek, Hazelwood, Missouri, USA). Antimicrobial susceptibility was tested by the Kirby–Bauer disk diffusion method and results interpreted according to the National Committee for Clinical Laboratory Standards criteria. Reappearance of signs of infection with the same organism(s) isolated in the dialysate within two weeks after the completion of antibiotic treatment was classified as relapse, and not as a new episode.

All Patients were on automated peritoneal dialysis (APD) and their dialytic prescription consisted of 1.36% and 2.27% glucose-based solutions Dianeal® over 9-10 hours night dwell and 7.5% icodextrin (Extraneal®, Baxter Castlebar, Ireland) 2 liters as the last fill for the day dwell. Total daily PD volume ranged between 10-12 liters with a fill volume ranging between 2.0-2.5 liters/cycle.

**Colonoscopy procedure**

In the procedure room, all patients were given supplemental oxygen (4 L/min) through a nasal cannula, and a 3-lead electrocardiogram, pulse oximetry, and blood pressure were monitored. Only the anesthesiologist certified in advanced life support and who completed a structured training program were permitted to administer propofol under the guidance of the endoscopist. The anesthesiologist who administered the sedative medications and physicians were present for the entire period of sedation and examination. The anesthesiologist attempted to achieve a level of sedation that allowed the patient to tolerate the procedure with minimal to mild pain while maintaining adequate cardiorespiratory function. Propofol induction of sedation was begun with an initial 40-mg bolus (20–30-mg for elderly and smaller patients at the discretion of the endoscopist and anesthesiologist) administered intravenously followed by titration with 10–20-mg boluses. After an initial bolus infusion of propofol, the patient was observed for 30–60 seconds before deciding to administer the next bolus. Fentanyl was administered intravenously in 12.5- or 25-g boluses and midazolam as 0.5–1.0-mg boluses. Additional medication
was titrated at 1–3-minute intervals to achieve or maintain the desired level of sedation. An endoscopy technician was available to assist the colonoscopy with technical maneuvers. This staffing pattern has been used in our endoscopy suite for all sedated procedures for several years and was not changed for the study. The following time points were recorded: initiation of sedation, full sedation (when the nurse and endoscopist mutually agreed the patient was sedated sufficiently to begin the procedure), colonoscope insertion, intubation of the cecum, and colonoscope removal from the anus. Interventional procedures like polypectomy were performed when indicated with disposable polypectomy forceps G-Flex. Post polypectomy bleeding (if any) was managed by epinephrine injection, hemoclip and heat probe. Biopsies were taken when indicated by disposable biopsy forceps (Endow by Olympus). After the procedure, both the physician and the nurse completed a questionnaire that assessed the patient’s level of sedation, pain, and ability to cooperate. Any complications (decline in oxygen saturation to less than 85%, heart rate less than 50 beats per minute, blood pressure less than 90/50 mm Hg, or need for mechanical ventilation) were recorded.

**Prophylactic antibiotic therapy**

Antibiotic prophylaxis in our center consisted of first-line antibiotic regimen for APD peritonitis was first- or second-generation cephalosporin plus an aminoglycoside, either tobramycin or netilmicin. Cefazolin combined with ceftazidime was also used as alternative.

**Peritonitis therapy**

Peritonitis episodes were treated with our center’s standard antibiotic protocol, which has been changed systematically over time. The first-line antibiotic regimen for APD peritonitis was first- or second-generation cephalosporin plus gentamicin (loading dose 60 mg i.v. + 4-5 mg/L intraperitoneal). Cefazolin or cefotixin (2 g i.v. + 50 mg/L intraperitoneal) combined with ceftazidime (2 g i.v. + 1 g intraperitoneal) was also used in our PD unit since the year 2010 according to the ISPD peritonitis guidelines (17). Vancomycin was used as a second-line therapy for primary nonresponding patients. Antibiotic regimens for individual patients were modified when culture results became available. Treatment usually lasted for either 2 weeks or at least 7 more days after normalization of the effluent WBC count, whichever was longer. Requirement of cessation of peritoneal dialysis, temporarily or permanently, and death during peritonitis, were defined as treatment failure. Heparin administration (500–1000 IU/L of dialysis fluid) and exchange of tubing was performed routinely in all cases of peritonitis. The indications for catheter removal included peritonitis caused by *Pseudomonas species*, peritonitis caused by fungi, cases with prolonged course or multiple recurrences, and episodes with suspected bowel perforation.

**Statistical methods**

Continuous variables are expressed as mean ± SD and categorical variables are expressed as percentage. Non parametric Spearman Rank test was used for continuous variables correlation and Mann-Whitney test used for comparison of two groups. P values were not adjusted for multiple testing and therefore should be considered descriptive. Variables with significant univariate associations were candidates for multivariate analysis. Univariate and multivariate analysis was used to study the relationship of age, sex, diabetes mellitus, time on APD, hemoglobin and albumin levels and prophylactic antibiotic use with post-colonoscopy peritonitis. The statistical analyses were limited to data regarding only the first episode of peritonitis, unless otherwise noted. Statistical significance was accepted at p < 0.05. The statistical analysis was performed using SPSS for Windows version 20 (*IBM Inc. New York, USA*).

**Results**

This prospective randomized study of patients with ESRD on APD and undergoing colonoscopy was performed according to *The Declaration of Helsinki* at King Fahd University Hospital, Al-Khobar, Saudi Arabia. The study was conducted from March 2012 throughout April 2016 with prior approval by *King Fahd Hospital Human Ethical committee*. All patients were above 18 years of age and written
informed consents were obtained from every patient after full explanation of the aim of the study, the complications of colonoscopy and the expected outcomes. Pregnant females, patients with ongoing sepsis, valvular or chronic heart disease, urinary tract infections, chronic liver disease, exit-site or tunnel infections, pneumonia or pulmonary tuberculosis, peritonitis or history of peritonitis for the last one year were excluded from the study (Figure-1). In a total of 134 APD patients included during the study period of 4 years, 96 colonoscopies were performed in 93 APD patients. Indications for repeating the procedure were inadequate preparation in one and partial or incomplete resection of a sessile polyp in two patients. Mean age was 62.3 ± 9.4 years and duration of dialysis was 35.2 ± 10.6 months; 34 (36.6%) patients were diabetics. The 93 APD patients included in the study were randomized into two groups; group-A (46 patients) who received cefazidine prophylaxis prior to colonoscopy and group-B (47 patients) who had colonoscopy without antibiotic prophylaxis. Randomization was 1:1. Demographic characteristics of patients are summarized in table-1. The two groups were age and sex matching. Diabetes mellitus was present in 34.8% and 38.3% and hypertension in 82.6% and 76.6% in the two groups respectively (p > 0.05). Mean duration of diabetes mellitus and the duration on APD was 18.8 ± 10.7 years and 20.5 ± 10.2 years, 31.1 ± 11.8 months and 30.6 ± 12.5 months in the groups A and B respectively (p > 0.05). The difference in overall fasting blood sugar (FBS) and hemoglobin A1-C (Hgb A1-C) was not statistically significant between the two groups (p > 0.05). At the time of colonoscopy, the mean blood urea nitrogen (BUN), serum creatinine and renal creatinine clearance were 44.18 ± 10.23 mg/dl and 46.12 ± 9.81 mg/dl; 8.28 ± 2.55 mg/dl and 8.33 ± 1.87 mg/dl; 6.3 ± 2.1 and 6.1 ± 2.8 ml/min in groups A and B respectively (p > 0.05). Mean hemoglobin level, serum potassium (K+) and serum albumin were similar in both groups at the time of the procedure (p > 0.05) (table-1). Indications for and findings of colonoscopy are summarized in table-2 and figure-2. Of all colonoscopies 60.2% showed normal findings, 17.2% with colonic polyps at different sites, 12.9% with angiodysplastic-like lesions, 5.4% with colonic ulcer (s), 3.2% with diverticula without diverticulitis and 1.1% had transverse colon stricture which was managed with stent insertion. Inflammatory bowel disease in the three patients was inactive for more than one year. Findings at colonoscopy are shown in figure-2. Post-colonoscopy peritonitis was documented in 2 (4.3%) and 3 (6.4%) patients in groups A and B respectively (p > 0.05); the causative organisms were mainly gram-negative bacteria (4 out of 5 cases were gram negative bacteria and one with Candida albicans) (table-3). Peritonitis episodes were not documented in any patient with diverticulosis or biopsied colonic polyps. All peritonitis cases resolved with treatment and one of the patients in group A required catheter removal because of fungal peritonitis. Complications other than peritonitis were 0.0% in both groups. Different variables were analyzed to demonstrate its relation with peritonitis episodes (Table-4). No significant difference in serum BUN or serum creatinine was observed between those who developed peritonitis and those who did not in the two groups (p > 0.05). Seven factors met the criteria for inclusion in the univariate analysis: age (≥ 60) (odds ratio [OR]=1.41, 95% confidence interval [95% CI]=1.11–1.6, P=0.0336), male sex (OR=0.79, 95% CI= 0.66–0.93, P= 0.0462), diabetes mellitus (OR=1.23, 95% CI=1.15–1.62, P=0.0389), duration on APD (OR=1.58, 95% CI=1.24–1.81, P=0.0308), hemoglobin level (OR=0.89, 95% CI=0.83–1.1, P= 0.0430), prophylactic antibiotics (OR=1.18, 95% CI=0.92–1.15, P=0.0481), and serum albumin (OR=2.24, 95% CI=1.98–2.66, P=0.0292). With multivariate analysis only age (OR=1.34, 95% CI=1.16–1.64, P=0.0326), diabetes mellitus (OR=0.79, 95% CI=0.68–0.81, P= 0.0279) and albumin levels (OR= 0.84, 95% CI= 1.12–1.36, P= 0.2253) were associated significantly with post colonoscopy peritonitis.

**Discussion**

Peritonitis remains the most serious complication of peritoneal dialysis. Around 18% of the infection-related mortality in PD patients is the result of peritonitis. Although less than 4% of peritonitis episodes result in death, peritonitis continues to be a leading factor to death in 16% of deaths on PD (18). In addition, peritonitis is probably the most common cause of technique failure in PD, and it remains a major cause of patients discontinuing PD and switching to hemodialysis. Therefore, the PD community continues to focus attention on prevention and treatment of PD-related infections (18-26). Peritonitis caused by enteral micro-organisms is relatively infrequent in PD patients (27-29). The source of contamination in those cases not associated with catheter exit-site or tunnel infections is thought to be
diverticular (1, 27). Micro-organisms can gain access to the peritoneum from the intestinal lumen or through genital organs (30, 31). Diagnostic instrumental procedures, such as colonoscopy, have been implicated in the development of these peritonitis episodes (14, 15). However, in many cases there is no evidence that links peritonitis to colonoscopy as a risk factor (29, 30). The recommendations concerned with colonoscopy in PD patients are not based solely on randomized controlled trials because such studies in PD patients are limited, where there is no definitive evidence but the group feels there is sufficient experience to suggest a certain approach, this is indicated as “opinion” based. The recommendations are not meant to be implemented in every situation but are recommendations only. Each center should examine its own pattern of infection, causative organisms, and sensitivities and adapt the protocols as necessary for local conditions (19). Post colonoscopy peritonitis in patients undergoing PD can result from translocation microorganisms across the bowel wall (32) and it has been alleged that gastrointestinal endoscopic procedures in those patients can lead to peritonitis (33). Contrary to Yip et al who, in a selected cohort of PD patients with indications of colonic examinations, suggested that diverticulosis, may be a risk factor for the development of enteric peritonitis, we did not encounter peritonitis episodes in our 3 diverticulosis patients. Colonic diverticulosis did not appear to affect the outcome of colonoscopy in our patients. Supporting our findings was the report by Toda et al. (34) who studied 317 PD-candidate patients over approximately 4 years and concluded that asymptomatic diverticulosis identified by computed tomography was not a risk factor for enteric peritonitis in their study population. A retrospective study by Tip et al. (35) found that the risk of peritonitis after colonoscopy without antibiotic prophylaxis was 6.3%. The authors however, indicated that it lacks statistical significance compared with prior antibiotic prophylaxis (35). Colon biopsy or polypectomy did not appear to further increase the risk of peritonitis in our cohort (11). Interestingly, the International Society for Peritoneal Dialysis recommended antibiotic prophylaxis before any procedure involving the abdomen or pelvis, including colonoscopy (16). Again, it is important to notice that these recommendations were based only on observational studies and case reports. The 2005 and the 2016 ISPD guidelines suggested empirical 1-gram ampicillin or aminoglycoside with or without metronidazole before colonoscopy (16, 36). These guidelines recommend antibiotic prophylaxis for CAPD patients undergoing colonoscopy with polypectomy; however, there has been little literature to support these recommendations. Studies on these guidelines are rare, and randomized controlled studies to support this recommendation are lacking. Moreover, these new guidelines clearly stated that the optimal antibiotic regimen has not been determined by clinical study yet (16). Similar suggestions were made by the Dutch Federation of Nephrology with the addition of dialysate drainage before the procedure (37). However, these suggestions have not gained wide acceptance. Contrary to the suggestions above, the American Society for Gastrointestinal Endoscopy and the British Society of Gastroenterology do not suggest prophylactic antibiotics before colonoscopy (38, 39). There exists a lack of consensus on this issue. There have been few case reports in the literature on peritonitis following colonoscopy in peritoneal dialysis patients (6, 7, 14-17). These reports suggested that instrumental procedures such as colonoscopy may precipitate gram-negative peritonitis in PD patients. On the other hand, some literature reported bacterial peritonitis following endoscopic polypectomy in peritoneal dialysis patients despite antibiotics prophylaxis (10). So far there are no strong data demonstrating a causal association between endoscopic procedures and bacteremia or that antibiotic prophylaxis prior to endoscopic procedures protects against bacteremia. Much of the existing data reflects estimated risk associated with conventional endoscopic techniques. There are no results available that confidently quantify bacteremia rates with newer endoscopic procedures such as per oral endoscopic myotomy, endoscopic submucosal dissection, flexible colonoscopy or polypectomy (11). We studied APD patients with and without antibiotic prophylaxis before flexible sigmoidoscopy. The difference in peritonitis episodes in our study between the two groups was not statistically significant (4.3% vs. 6.4%, p > 0.05). Surprisingly, none of the post-polypectomy and none of our patients with diverticular disease (without diverticulitis) had post-procedure peritonitis in our cohort; finding that correlates with the report of Yip, et al. (11) who stated that colonic biopsy or polypectomy was not associated with a higher risk of peritonitis in their CAPD patients. In addition, we did not encounter serious complications of colonoscopy i.e. perforation or hemorrhage. Transient bacteremia occurs frequently during routine daily activity, often at rates exceeding those associated with endoscopic
procedures. Brushing and flossing of teeth has been associated with rates of bacteremia of 20% to 68%, use of toothpicks with rates of 20% to 40%, and even activity that might be considered entirely physiologic, such as chewing food, with rates ranging from 7% to 51% (40). By multivariate analysis, the use of prophylactic antibiotics prior to colonoscopy was not a predictive variable for developing peritonitis in our study population, on the contrary, other factors namely age, diabetes mellitus and serum albumin levels proved to be significant predictive variables for post-colonoscopy peritonitis. One patient from the group of those who received prophylactic antibiotics had Candida species in peritoneal fluid culture. Although we could not prove the relation between antibiotic prophylaxis and the development of this un-expected growth, it is not unreasonable to speculate that antibiotic administration may have favored intestinal non-bacterial overgrowth (Candida in our case) which, potentially, may have conditioned the pathogenicity of these organisms in that patient. The human colonic microflora ecosystem, its metabolic functions, and its colonization resistance are vital for the well-being of the host, production of vital metabolites, and prevention of infection. In a study by Edlund and Nord (41) marked ecological disturbances were seen in the intestinal microflora during antibiotic treatment. The numbers of enterococci, enterobacteria (except E. coli) and peptostreptococcus increased significantly during treatment. Eight patients became newly colonized by Klebsiella spp. and Citrobacter freundii during treatment. The number of patients colonized with yeasts (mostly C. albicans) increased from zero to nine during treatment; two patients were still colonized with yeasts after treatment. Sullivan et al (42, 43) reported that administration of antimicrobial agents, therapeutically or as prophylaxis, causes disturbances in the ecological balance between the host and the normal intestinal microflora and that by using antimicrobial agents, the risk of emergence and spread of resistant strains between patients and dissemination of resistant micro-organisms increases significantly. In a study concerned with a similar matter, Berg (44) concluded that the colonic microflora appears to stimulate the host immune system to respond rapidly to pathogen challenges. Although the cells of the intestinal tract coexist with the normal commensal microflora, they recognize and clear invading pathogens before returning to homeostasis with the commensal bacteria. The colonic microflora provides a number of benefits, including contributing to the host’s nutrition and protecting the host from infection. In most cases of antimicrobial prophylaxis or therapy, the bacterial populations in some genera are reduced in numbers while those in other genera increase. In some cases, the increased numbers of certain bacteria are accompanied by resistant strains of bacteria or overgrowth by fungi. Treatment with antimicrobial combinations does not necessarily prevent resistance development. It may even result in fungal overgrowth and appearance of bacteria with resistance to all of the drugs in the combination (45). Given the notorious possibility of resistant strains’ development and the relative rarity with which most PD patients undergo colonoscopy procedures, the frequency and risk of colonoscopy-related bacteremia, as we demonstrated in our study, is trivial compared with the frequency of bacteremia encountered with routine daily activity. This provides a strong rationale against routine administration of antibiotic prophylaxis prior to all endoscopic procedures.

There are some limitations, however, in our study. First, this study was conducted in a single tertiary medical center, and endoscopy-associated complications may vary in different hospitals. Second, the study was conducted on a selected group of APD patients after applying strict exclusion criteria. Third, the study recorded only 93 endoscopic procedures and may have underestimated the importance of antibiotic prophylaxis. Therefore, larger randomized trials are required to explore the necessity of antibiotic prophylaxis in the prevention of postcolonoscopy PD peritonitis. Nevertheless, our study has the strength of being the first prospective randomized study in this field.

**Conclusion**

The relation between prophylactic antibiotic use prior to colonoscopy in APD patients was lacking and the overall risk of peritonitis in general is low in this population. Only old age, diabetes mellitus and low serum albumin appeared to be of significance. Neither polypectomy; partial or complete nor diverticulosis were associated with increased incidence of post-colonoscopy peritonitis. The study, however, the study recorded limited number of patients and may have underestimated the importance of antibiotic prophylaxis. Therefore, larger prospective randomized trials are needed.
Table 1. Demographic characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 46)</th>
<th>Group B (n = 47)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>61 ± 12.5</td>
<td>63 ± 11.8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Female/Male (female %)</td>
<td>11/35 (31.4)</td>
<td>13/34 (38.2)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>21.7</td>
<td>19.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>38 (82.6)</td>
<td>36 (76.6)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>BMI at beginning, mean ± SD</td>
<td>29.1 ± 4.1</td>
<td>29.3 ± 3.8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>16 (34.8)</td>
<td>18 (38.3)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Duration of diabetes, (years), mean ± SD</td>
<td>18.8 ± 10.7</td>
<td>20.5 ± 10.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Duration on APD, months (mean ± SD)</td>
<td>31.1 ± 11.8</td>
<td>30.6 ± 12.5</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Overall FBS in diabetics, mmol/L (mean ± SD)</td>
<td>8.6 ± 1.3</td>
<td>8.4 ± 1.4</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Overall Hgb A1C % in diabetics (mean ± SD)</td>
<td>7.1% ± 0.5</td>
<td>6.8 ± 0.8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hgb at colonoscopy, gm/dl (mean ± SD)</td>
<td>10.16 ± 2.25</td>
<td>10.32 ± 2.77</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>BUN at colonoscopy, mg/dl (mean ± SD)</td>
<td>44.18 ± 10.23</td>
<td>46.12 ± 9.81</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Serum Cr. at colonoscopy, mg/dl (mean ± SD)</td>
<td>8.28 ± 2.55</td>
<td>8.33 ± 1.87</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Serum K+ (mEq/L)</td>
<td>4.1 ± 1.9</td>
<td>3.9 ± 2.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Serum albumin (gm/l)</td>
<td>3.8 ± 2.0</td>
<td>3.7 ± 1.8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Renal Cr Cl. ml/m (mean ± SD)</td>
<td>6.3 ± 2.1</td>
<td>6.1 ± 2.8</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>


Table 2. Indications for and findings of colonoscopy

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Indication</th>
<th>Findings (number)</th>
<th>Action (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 (18.3)</td>
<td>Screening for colonic Cancer</td>
<td>Normal (13) Transverse and descending colon polyps (4)</td>
<td>None (13) Biopsies and removal (4)</td>
</tr>
<tr>
<td>15 (16.1)</td>
<td>Investigation for iron deficiency anemia</td>
<td>Normal (11) Angiodysplastic like lesions (4)</td>
<td>None (11) Biopsies &amp; bleeding protocol (4)</td>
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<tr>
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<td>Altered bowel habits (chronic diarrhea or chronic constipation)</td>
<td>Normal (9) Diverticulae (3) Transverse colon polyps (2)</td>
<td>None (9) None (3) Biopsies and removal (2)</td>
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<td>Positive fecal occult blood testing without overt rectal bleeding</td>
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<tr>
<td>9 (9.7)</td>
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<td>Normal (1) Transverse or descending colon ulcers (2)</td>
<td>None (1) Biopsies &amp; bleeding protocol (2)</td>
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</table>
Angiodysplastic-like lesions 
(3) Ascending & transverse colon polyp (3)

Biopsies & bleeding protocol (3) Biopsies and removal (3)

8 (8.6) Finding of polyp (s) during sigmoidoscopy Normal (5) Descending colon polyps (2) Angiodysplastic-like lesions (1)

Biopsies and removal (2) Biopsies & bleeding protocol (1)

8 (8.6) Bloody effluent Normal (7) Transverse colon polyp (1)

None (7) Biopsies and removal (1)

7 (7.5) Family history of colon cancer or polyps Normal (5) Ascending colon polyp (1) Descending colon ulcer (1)

None (5) Biopsies and removal (1) Biopsies (1)

3 (3.2) Inflammatory bowel disease Transverse and/or descending colon ulcers (2) Transverse colon stricture (1)

Biopsies (2) Stent (1)

<table>
<thead>
<tr>
<th>Table 3. Microorganisms responsible for peritonitis</th>
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<table>
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<th>Table 4. Comparison of characteristics of patients with and without peritonitis after colonoscopy</th>
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<tr>
<td>Number (%)</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>2 (4.3) 44 (95.7)</td>
</tr>
<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Duration on APD, month, (mean)</td>
</tr>
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<td>BUN, mg/dl (mean)</td>
</tr>
<tr>
<td>Creatinine, mg/dl (mean)</td>
</tr>
<tr>
<td>Hemoglobin, gm/dl (mean)</td>
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<tr>
<td>Serum K+, mEq/l (mean)</td>
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<tr>
<td>Serum albumin, gm/dl (mean)</td>
</tr>
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</table>
Figure 1. Consort diagram demonstrating study design and patients' progress.

CHD: chronic or valvular heart disease, UTI: urinary tract infection, CLD: chronic liver disease, peritonitis: ongoing or previous.

Figure 2. Finding of colonoscopies in the study population

ADL: Angiodysplastic-like lesions
References


Study the Effects of Vernakalant on Ischemic-Reperfusion Dysrhythmias in Experimental Animals in Comparison with Amiodarone

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Abstract

Cardiac dysrhythmia is a term for any of large heterogeneous group of conditions in which there is abnormal electrical activity in the heart. Dysrhythmias may be life threatening medical emergencies that can result in cardiac arrest and sudden death; it may predispose the patient to potentially life threatening stroke and embolism.

The pathogenesis of cardiac dysrhythmia involves crossing of electrolytes through different ions channels on the cellular level that may be dysrhythmogenic.

In this study, ischemic-reperfusion dysrhythmia were performed in experimental animals, ischemia of the myocardium results in release of ischemic metabolites and slowing impulse propagation while reperfusion results in increase late inward Na current (INaL) which amplifies Na⁺ influx and intracellular Na⁺ concentration leading finally to calcium overload. The enhancement of Na⁺ and Ca²⁺ concentration causes electrophysiological instability, formation of free oxygen radicle and liberation of platelet activating factor.

Seeking for novel antidysrhythmogenic agents having ions channels inhibiting properties, this work aims to investigate the effects of vernakalant, antidysrhythmic drug with atrial selective and multi-channel blocking effect on ischemia-reperfusion dysrhythmia in experimental animals in comparison with amiodarone as a standard antidysrhythmic medication.

Keywords: Ischemic-Reperfusion Dysrhythmia, Vernakalant & Amiodarone.

Introduction

Dysrhythmia is an abnormality of the rate, rhythm, site of origin of heart impulses or a hindrance in electrical conductive system of the heart that develop activation sequences of myocardium. The impulses of conductivity originate from the primary pacemaker, sinus node, spontaneously sending depolarization wave through the atrium, depolarizing the atrioventricular node then propagated to Purkinje fibres then depolarizing the ventricle in a systemic manner. Actually, there are more than hundred classes of cardiac dysrhythmias. The normal cardiac rhythm, sinus rhythm, could be disrupted due to failure of automaticity, such as sick sinus syndrome or due to over activity, such as inappropriate sinus tachycardia.

Ectopic foci cause premature excitation of the myocardium on single or continues basis leading to premature atrial contractions (PACs) and premature ventricular contractions (PVCs). Another classes of dysrhythmia, atrial fibrillation, paroxysmal atrial tachycardia (PAT) and supraventricular tachycardia (SVT), caused by micro or macro re-entry. In general, the seriousness of cardiac dysrhythmias depends on the presence or absence of structural heart diseases. [Fu, 2015]

The most common relatively benign dysrhythmia are atrial fibrillation, PACs and PVCs, being benign is in case of absence of structural heart lesion. In contrast, the presence of non-sustained ventricular tachycardia (VT) or syncope in coronary heart disease patient may be a harbinger of subsequent cardiac death and must not be ignored.
The most frequent complaints associated with cardiac dysrhythmia, dizziness, palpitations and syncop are noticed either by family physician or by the patient himself. On the contrary, these ubiquitous complaints, sudden cardiac death remains an important public health concern.

Centres for Disease Control and Prevention (CDC) have estimated sudden cardiac death in more than 600,000 per year. Up to 50% of patient have sudden death as the first manifestation of cardiac disease. [Grant, et al 2012]

Cardiac electrophysiology

The action potential of ventricular myocytes is the standard model of cardiac action potential and it is composed of 5 phases (numbered from 0-4). Figure 1 [Rudy, 2008] Phase 4 is the resting membrane potential, the cell is not being stimulated, when an electric current from the adjacent cell typically stimulates cardiac myocytes, a sequence of influx and efflux of various anions and cations that produce action potential of cardiac cells propagating the electric stimulation to different parts of the myocardium.

The resting membrane potential is caused by different ionic concentration and conductance through the cell membrane during phase 4 of the action potential. The normal resting membrane potential in ventricular myocardium is about -85 to -95 mV. This potential is determined by selective permeability of the cell membrane to different types of electrolytes. The cell membrane is most permeable to K⁺ ions and relatively impermeable to the other ions. The resting membrane potential is there for dominated by the K⁺ equilibrium potential according to K⁺ gradient across the cell membrane. The membrane potential can be calculated using Goldman-Hodgkin-Katz voltage equation. [Grunnet, 2010] The stability of electrical gradient is maintained by different ions pump and exchange mechanism, involving Na⁺/K⁺ ion exchange pump, Na⁺/Ca⁺ exchanger current and Inwardly Rectifying K⁺ current (Ikr). [Sipido, et al 2007].

Phase 0 is a rapid depolarization phase. The slope of phase 0 represents the maximum rate of depolarization of the cell and is known as dV/dt max. This phase is caused by fast opening of Na⁺ channels leading to rapid Na⁺ influx (I_{Na}) into the cell. The ability of the cardiac cells to open fast Na⁺ channels during phase 0 is related to the membrane potential at the moment of excitation. If the membrane potential is at its baseline (about -85 mV), all the fast Na⁺ channels are closed and the excitation will open them all causing large influx of Na⁺ ions. If the membrane potential is less negative, some of the fast Na⁺ channels will be inactivated and insensitive to opening, leading to lesser response to excitation of the cell membrane and a lower Vmax, thus the resting membrane potential become too positive, so that lead to delayed excitation and conduction, increasing risk for dysrhythmias. [Santana, et al 2010a].

The fast Na⁺ channels are being controlled by numbers of gates, each gate can attain a value between 1 (fully open) and 0 (fully closed). The product of all gates denotes the percentage of channels available to conduct Na⁺. According to Hodgkin and Huxley model, the Na⁺ channels
contains 3 gates: m, h and j. In the resting state, m gate is closed (zero) and h and j gates are open (one). Upon electric stimulation of cardiac myocytes, m gates opens quickly while simultaneously h and j gates close more slowly. For a brief period of time, all gates are open (non-zero) and Na⁺ enter the cell following electrochemical gradient, thus, if the resting membrane potential is too positive, the h or j gates may be considerably less than one, such that the product of m, h and j becomes too small upon depolarization. [Grunnet, 2010].

Phase 1 action potential is due to inactivation of Na⁺ channels. The transient net outward current causing small downward deflection of the action potential is due to movement of K⁺ and Cl⁻ ions, carried by I_{to1} and I_{to2} currents respectively. Particularly the I_{to1} contributes to the notch of ventricular myocytes action potentials. [Santana, et al 2010b].

The plateau phase of cardiac action potential is maintained by balance between inward movement of Ca⁺ (ICa⁺) through L-type calcium channel and outward movement of K⁺ ions through the slow delayed rectifier K⁺ channels (IKs). [Grunnet, 2010] During phase 3 (rapid repolarization), the L-type calcium channels are closed while the slow delayed rectifier K⁺ channel are still open. This ensure a net outward current, corresponding to negative change in membrane potential, thus allowing more types of K⁺ channels to open. These are primarily the rapid delayed rectifier K⁺ channels (IKr) and the inwardly rectifier K⁺ current (IK₁). This net outward, positive current (equal to loss of positive charge from the cell) cause the cell to depolarize. The delayed rectifier K⁺ channels close when the membrane potential is restored to about -80 to -85 mV, while IK₁ remains conducting throughout phase 4, contributing to set the resting membrane potential. [Kubo, et al 2005].

Pathophysiology of dysrhythmia

The pathogenesis of dysrhythmia is involving three main mechanisms: enhance or supressed automaticity, triggered activity or re-entry. Automaticity is a natural property of cardiac myocytes, suppression of automaticity of sinoatrial node (SAN) can lead to sinus node dysfunction and sick sinus syndrome (SSS) which is the most common indication for permanent pacemaker implantation. In contrast, enhance automaticity can result in multiple dysrhythmias, both atrial and ventricular. Triggered activity occurs in case of early afterdepolarization and delayed afterdepolarization initiate spontaneous multiple depolarization precipitating ventricular dysrhythmia such as Torsades de pointes and digitalis induced ventricular dysrhythmia. Probably, the most common mechanism of arrhythmogenesis results from re-entry that include bidirectional conduction and unidirectional block. “Micro” level re-entry results in ventricular tachycardia from conduction around the scar of myocardial infarction and “Macro” level of re-entry results in conduction through Wolff-Parkinson-White [WPW] syndrome concealed accessory pathway. [Nakagawa, et al 2001]

Atrial fibrillation is the most common type of supra-ventricular dysrhythmia (SVD) associated with significant morbidity, mortality and affecting quality of life. [Camm, et al 2012] Despite significant progress in catheter and surgical ablation techniques, antidysrhythmic drugs remain first line therapy for rhythm control. [Fragakis & Katritsis, 2012] Currently available and commonly used antidysrhythmic drugs are limited by incomplete efficacy for achieving and maintaining sinus rhythm and/or by adverse effects such as life threatening ventricular pro-dysrhythmia or severe extra-cardiac toxicities. [Lafuente, et al 2006] [Camm, 2012] Amiodarone is the most effective medication for rhythm control but it is often discontinued due to numerous systemic side effects such as thyroid and lung dysfunction. [Lafuente, et al 2006] [Camm, 2012] Therefor, there is a clear need for safer and more effective pharmacological strategies for rhythm control. [Dobrev & Nattel, 2010] In light of these unmet needs, the following research has been focused to design novel pharmacological target aiming to treat most common type of SVD (atrial fibrillation) with higher efficacy and less risk. An attractive prospect for AF therapy has been considered the introduction of agents with selective affinity to ions channels specifically or predominately involved in atrium. [Dobrev, et al 2010]

Indeed, this research is currently focused on the development of agent targeting to modification of those pathway and molecular mediators which are involved in propagation and maintenance of supraventricular dysrhythmias. [Fedida, et al 2005]
Vernakalant

Vernakalant has highly selective atrial ion-channel blocking properties that has recently involved in management of acute atrial fibrillation (AF). [Dobrev & Nattel, 2010] [Dobrev, et al 2010] Intravenous vernakalant has been approved for the alteration of recent-onset AF in Europe and other parts of the world, but not in the USA. Vernakalant inhibits atrial-selective K+ currents, including the ultra-rapidly activating delayed rectifier K+ current (IKur) and acetylcholine-activated inward rectifier K+ current (IK,ACH), and causes rate-dependent atrial-preferential Na+ channel block, with only a small inhibitory effect on the rapidly activating delayed rectifier K+ current (IK) in the ventricle.[Fedida, et al 2005] Due to its atrial-selective properties, vernakalant prolongs the effective refractory period (ERP) of the atria with moderate effects on the ventricles [Dorian, et al 2007] which explains the low pro-dysrhythmic risk for torsades de pointes (TdP) dysrhythmias. [Dobrev & Nattel, 2010] [Dobrev, et al 2010].

Vernakalant is an antidysrhythmic agent that has predominant properties on supraventricular electrophysiology. A human electrophysiological study demonstrated that vernakalant infusion dose-dependently prolongs atrial ERP. [Dorian, et al 2007] Atrial selectivity, thereby avoiding ventricular pro-dysrhythmia, can be achieved by aiming towards atrial-selective channels, such as IKur and IK,ACH, by atrial-preferential inhibition of excitability through exploiting state-selective Na+ channel blocking properties or by high selectivity for rapid rhythms like AF. [Dobrev & Nattel, 2010]

Vernakalant blocks several K+ channels. It inhibits IKur in the open state, with preserved efficacy at high stimulation frequencies. [Fedida, et al 2005] The atrial-selective IK,ACH current is potently blocked by vernakalant. [Fedida, 2007] [Wettwer, et al 2013] Vernakalant also targets Kv4.3 and human ERG (hERG) channels that correspond to the transient outward current (Ito) and IK, respectively, although the contribution of Ito to repolarization is lower in ventricles than in atria. [Fedida, et al 2005] In contrast, IK is an important repolarizing current in ventricular cells. Its blockade causes QT interval and action potential duration prolongation, predisposing to TdP arrhythmias through the development of dysrhythmia-triggering early afterdepolarization and/or an increased dispersion of repolarization. [Dobrev & Nattel, 2010] However, the potency of vernakalant in blocking hERG channels is up to 100-fold lower than that of class IC antiarrhythmic drugs (flecainide or propafenone). [Fedida, et al 2005] Late Na+ current (INa,late) inhibition by vernakalant is protective against the proarrhythmia from IK blockade. [Orth, et al 2006]

Vernakalant causes an open-channel block of Na+ channel Nav1.5 α-subunits that underlie the atrial IKur. [16] [18] At physiological heart rates, the block of Nav1.5 channels by vernakalant is weak because of its rapid unbinding kinetics from the channel, [Fedida, et al 2005] [Fedida, 2007] which is consistent with the small increase in QRS interval (a marker of ventricular conduction velocity) observed in clinical trials. [Roy, et al 2008] [Pratt, et al 2010] [Carmeliet & Mubagwa, 1998] In addition, the effects of vernakalant on Na+ channels are voltage and rate dependent, resulting in an enhanced inhibitory potency at depolarized potentials and rapid rates, like in fibrillating atria. [Fedida, et al 2005] The resting membrane potential of normal atrial myocytes is 10 mV more depolarized than that of normal ventricular myocytes. When atrial myocytes fail to repolarize fully, as can happen during AF, the atiroventricular difference in resting membrane potential is further accentuated and a large fraction of atrial Na+ channels is inactivated. This reduces the Na+ channel reserve predominantly in the atria and allows vernakalant to inhibit preferentially atrial Na+ channels. [Fedida, et al 2005] Although such voltage and rate dependency is also typical for flecainide and propafenone, they do not show atrial selectively, [Fedida, et al 2006] [Carmeliet & Mubagwa, 1998] and the important difference is that vernakalant exhibits rapid unbinding kinetics from Na+ channels. [Tropp-Pedersen, et al 2001] Therefore, Na+ channel block with rapid unbinding kinetics has recently been identified as a promising option for atrial-selective drug treatment of AF. [Comtois, et al 2008] [Antzelevitch, et al 2010]

Amiodarone

Amiodarone is a broad spectrum anti-dysrhythmic drug against numerous types of irregular heartbeats including ventricular tachycardia, ventricular fibrillation, atrial fibrillation & paroxysmal supraventricular tachycardia. [Porid, 1995]
The antiarrhythmic effect of amiodarone is due to non-competitive alpha and beta adrenergic inhibition, class II activity, in addition, amiodarone is a very effective blocker of sodium channels, class I activity, moreover, it has a week calcium channel blocking effect, class IV activity. [Du, et al 1995]

Amiodarone increases the cardiac refractory period without influencing resting membrane potential, except in automatic cells where the slope of pre-potential is reduced, generally reducing automaticity [Varro & Robloczky, 1986]. Amiodarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (after load) and slightly increases cardiac index. [Singh, 1970] After oral dosing, however, amiodarone produces no significant changes in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF. [Twidale, et al 1993] After acute intravenous dosing in man, amiodarone may have a mild negative inotropic effect. [Gangol, et al 1985]

Amiodarone does not alter vagal reflexes or the responsiveness of cardiac cholinergic receptors but it causes some non-competitive alpha and beta adrenergic blockade. [Biggera & Hoffman, 1992] Amiodarone has also a selective inhibition of the effect of T3 on myocardium that may contribute to prolongation of the action potential duration and refractoriness. [Melmed, et al 1981]

The Pharmacokinetic of numerous drugs, including many that are commonly administered to individuals with heart disease, is affected by amiodarone. Particularly, doses of digoxin should be halved in individuals taking amiodarone since amiodarone decreases renal and non-renal clearance of the digitalis glycosides and increases its bioavailability. These effects appear related to the dose of amiodarone, with higher doses of amiodarone being associated with the greatest increase in digoxin concentration. [Achilli & Serra, 1981]

Amiodarone potentiates the action of warfarin. Individuals taking both of these medications should have their warfarin dose halved and their anticoagulation status, measured as prothrombin time & international normalized ratio, measured more frequently. Amiodarone decreased the total body clearance of warfarin in normal subjects but did not change volumes of distribution. Amiodarone is a general inhibitor of the cytochrome P450 catalyzed oxidation of warfarin. [Larry, et al 1991]

The FDA revised the labels of amiodarone and simvastatin in 2002 to warn of increased risk of rhabdomyolysis, the most severe form of myopathy, when the two drugs are taken concomitantly in doses greater than 20 mg per day of simvastatin. [Karimi, et al 2010] There are many other drugs should not be taken with amiodarone: cimetidine, clopidogrel, cyclosporine, dextromethorphan, diclofenac, loratedine, a beta-blocker, potentiation, and Ca2+ channel blockers. [Singh, et al 1989]

Amiodarone has numerous side effects. Most individuals administered amiodarone on a chronic basis will experience at least one side effect [Vanerven & Schalij, 2010]. Decrease heart rate and increase incidence of heart block, interstitial lung disease, Some individuals developed pulmonary fibrosis after a week of treatment, Amiodarone is structurally similar to thyroxin, which contributes to the effects of amiodarone on thyroid function, both under and over activity of the thyroid may occur on amiodarone treatment [Batcher, et al 1989]. Corneal micro-deposits, Corneal verticillata, Abnormal liver enzyme results are common in patients on amiodarone. [Flaharty, et al 1989]

According to the numerous drug interactions and adverse effects caused by amiodarone, this research investigates the effect of a novel antidysrhythmic drug, vernakalant, on reperfusion dysrhythmia in rats in comparison with amiodarone, standard broad spectrum antidysrhythmic drug.

Material and method

The animals used in the experiments were 40 adult male albino rats weighting 170-200 g. The animals were handled according to the guide lines of local ethical committee which comply with the international laws for use and care of laboratory animals.

The animals were divided into four groups, each group contained 10 rats.
- (Control Group I) normal (did not receive any medications)
- (Control Group II) diseased group (reperfusion dysrhythmia, adult male rats were anaesthetized by intramuscular injection of 25% solution of urethane in a dose of 0.7ml/100g body weight. The trachea was exposed and tracheotomy was done through which a Y-shaped glass tube was cannulated. The animal was artificially ventilated in a respiratory rate of 40/minute and tidal
volume of 6 ml/kg [Harkness & Wagner, 1989] throughout the experiment to avoid any respiratory disturbances during the experiment.

The left jugular vein was cannulated by pediatric cannula (size 24G). The chest was opened by midline thoracotomy at the xiphesternal junction. After opening the pericardium, the heart is exteriorized by gentle pressure on the chest wall then a snap was taken by a proline 5-0 thread around left anterior descending branch of the left main coronary artery and the two ends of the thread were put into a plastic tube closed by a clamp for 15 min & subsequent reperfusions for 30 min. [Abraham, et al 1989]

- (Group III) received vernakalant after induction of dysrhythmia (after 30 minutes reperfusion) by a 10-minute infusion of 3 mg/kg followed by a 15-minute observation period then a second 10-minute infusion of 2 mg/kg if still in AF. [Tian & Frishman, 2011]
- (Group IV) received amiodarone 100 mg IV [loading dose] approximately 30 min prior to induction of dysrhythmia. [Nadkarni, et al 2010]

In all groups, limb electrodes of the electrocardiogram recorder of the power lab device were connected to three limbs of the animal with the following order:
- The negative electrode (black) is connected to the right upper limb.
- The positive electrode (red) is connected to the left lower limb.
- The indifferent electrode (green) is connected to the left upper limb.

The standard lead II was adjusted by the power lab and the heart rate was recorded by the power lab device (Model no. 866. MLA1215 Animal Bio AMP lead wires set of three 2 mm pins to micro hook lead wires).

Animals were anesthetized and prepared as the previous groups. After recording of normal ECG, reperfusion dysrhythmia was induced in the same previous manner with ECG recording every 5 minutes From T0 to T23.

For each animal, the heart rate, time of appearance of cardiac dysrhythmias and disturbances ECG were recorded.

Statistical methods

Data were statistically described in terms of range, mean ± standard deviation (± SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Kruskal Wallis analysis of variance (ANOVA) test. For comparing categorical data, Chi square ($\chi^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value ($p$ value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Control group I

Heart rate

The normal heart rate ranged between 226 and 312 beats/minute, with a mean ± SD of 286.20 ±26.377 ranged from T0-T23.

S-T segment

There were no significant changes in the S-T segment with normal ECG. (Figure 2)
Control group II

Heart rate

By induction of dysrhythmia, there were no statistically significant changes in heart rate up to the T4 (Closure of coronary arteries). From T5 (Reperfusion), there was statistically significant reduction in heart rate down to the T 23,177.5±14.849 with a ratio of reduction of 38%. (Figure 3)

S-T segment

There were no significant changes in the S-T segment before induction of dysrhythmia, T0-T4. Reperfusion produced an equal percentage of S-T segment depression (Figure 4) and elevation (Figure 5) about 10% for each at T5 and then there was statistically significant increase in the percentage of S-T segment depression to reaches 60% at T9 then decreased gradually from T14, 50%, to reach 0% at T23. The percentage of elevated S-T segment increased gradually to reach 66% at T22.
Figure 4. Depressed S-T segment occurred at T 9 at control group II.

Figure 5. Elevated S-T segment occurred at T 12 at control group II

Dysrhythmia

Coronaries reperfusion resulted in induction of dysrhythmia starting with the T5 in 2 animals, 20%, in the form of SVEs and SVT in one animal and VEs in the second animal. The incidence of dysrhythmias increased gradually to affect all animals (100%) by T9. Death of the animals started to occur after T12 in one animal, 10%, and increased gradually to reach 40% after T20. As regards the types of reperfusion dysrhythmia to the non-treated rats, control group I, the following four types of cardiac dysrhythmias developed, ventricular tachycardia (V.T.) (Figure 6), multiple ventricular extra systoles (V.Es) (Figure 7), multiple supraventricular extra systoles (S.V.Es) (Figure 8) and supraventricular tachycardia (S.V.T) (Figure 9).
Figure 6. Ventricular tachycardia

Figure 7. Ventricular extrasystole
Figure 8. Supraventricular extrasystole

Figure 9. Supraventricular Tachycardia

Table 1. Summary of types of coronaries reperfusion dysrhythmias

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<td>SVE+SVT</td>
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<td>VT</td>
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<td>T10</td>
<td>SVE+SVT</td>
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<td>VE+VT</td>
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</table>
Comparison between group III (Vernakalant treated group) & group IV (Amiodarone treated group) against group II (reperfusion dysrhythmias)

Heart rate

There were no statistically significant differences in the resting heart rate, T0, between control group II, both group III and IV. By induction of dysrhythmia in group III, vernakalant reduced bradycardia gradually from 38% to 18.5% (Figure 10), while in group IV, amiodarone decreased the bradycardia from 38% to 17.5% (Figure 11).

Figure 10. Different heart rate changes in group III
S-T segment

There are no significant changes in the S-T segment before induction of dysrhythmia, T0 –T4 in the control group II and both group III and group IV. There was slight increase in the percentage of elevated S-T segment starting from T5 to T10 on comparison between the control group II and group III, then this percentage gone within normal range with the control group with no statistically significant changes up to T 23. In group IV, the percentage of elevated S-T segment markedly decrease to reach 0% during the whole experiment and the percentage of normal S-T segment stays at a high level ranged from 100% at T5 to 80% at T23 with statistically significant changes starting from T7 to T21 (Table 2).
Table 2. Comparison between groups II, group III, group IV the percentage of normal, elevated and depressed S-T segment

<table>
<thead>
<tr>
<th>Time</th>
<th>Group II Normal</th>
<th>Elevated</th>
<th>Depressed</th>
<th>Group III Normal</th>
<th>Elevated</th>
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</table>
Dysrhythmias

There were regularly paced complexes with normal shape without any statistically significant differences between group II, group III and group IV up to T4.

In group III and IV, the heart rate stayed regular all up to T23. There were statistically significant changes in the regularity of the heart beats between the control group II and both group III and IV starting from T7 until T23.

VT appeared only in one animal at T22 in group III, while in group IV, there were not any types of dysrhythmia occurred all through adrenaline doses. (Figure 12)

![Figure 12. Chart showing percentage of different types of cardiac dysrhythmias in group II, III and IV.](image)

Discussion

Cardiac dysrhythmias occur when the electrical signals to the heartbeats are not working probably. For instance, some people experience irregular heartbeats, which may feel like a racing heart or fluttering. Many types of cardiac dysrhythmias are harmless, however, if they are particular abnormalities resulting from weak or damage heart, dysrhythmia can cause serious and even potentially fatal symptoms. Dysrhythmias are life threatening medical emergencies that may cause cardiac arrest and sudden death. Up to 65% of patients had sudden cardiac death as first manifestation of cardiac dysrhythmia. In the United States, more than 850,000 people are hospitalized for a dysrhythmia each year. [John, et al 2010]

Supraventricular dysrhythmia is a complicated type of dysrhythmia that is hard to treat with habitual antidysrhythmic medications. Novel pharmacological methodologies are in advance concentrated on the advancement of specialists with selective affinity to ion channels predominately engaged with the atrium. In parallel, inquire about endeavors have been focused on the development of agents focusing to adjustment of those pathways which are associated with the proliferation and maintenance of atrial fibrillation (AF). [Ferrari, et al 2015]

Novel ion channels inhibition agents developed to treat AF are broadly separated into two categories such as “atrial-selective” compounds and “multi-channel blockers”. Vernakalant is predominantly “atrial-selective” blocker while amiodarone is considered as a “multi-channel blocker”.

Vernakalant is an antiarrhythmic atrial-selective compound acting by blockade of IKur, which is exclusively expressed in the atria. Furthermore, it is a multichannel blocker that affects the sodium channel and IK-Ach both expressed predominantly in the atria. [Burashnihov, et al 2010]

This study aimed to investigate the possible antidysrhythmic effect of vernakalant on coronary reperfusion cardiac dysrhythmias, in comparison with amiodarone. In this work, adult male albino rats were used. Their heart structure is relatively close to that of the humans and their size made it easy to induce ischemia-induced dysrhythmias. Amiodarone was chosen as a comparator, because it is a standard antidysrhythmic drug with broad spectrum properties against different types of cardiac dysrhythmia with different mechanisms.
In this work, adult male albino rats weighting 170-200 g were kept in normal environment without any procedures or medications given, as a standard (control) group I with normal heart rate and normal ECG recording.

In group II (diseased group), It was noticed that there is no changes in heart rate during closure of coronary arteries (up to T4), after reperfusion (T5) there was statistically significant reduction in the heart rate with irregular cardiac rhythm, it was explained by [Jurkoviciova and Cagan, 1998] that abnormal cardiac rhythm originate as a consequence of the complex of cellular and humeral reactions accompanying the opening of coronary artery leading to release of chemical substances such as calcium, thrombin, platelet activating factor, inositol triphosphate & angiotensin II which operate as modulators of cellular electrophysiology causing complex changes at the level of ions channels.

In vernakalant treated group III the resting heart rate did not differ significantly from that of the control group I, vernakalant reduced the coronary-reperfusion induced bradycardia from 38% to 18.5%. It was stated by [Bechard et al, 2011] that vernakalant is an antiarrhythmic atrial-selective compound acting by blockade of IKur, which is exclusively expressed in the atria. Furthermore, it is a multichannel blocker which affects the sodium channel and IK-Ach both expressed predominantly in the atria. Inhibiting potassium currents, vernakalant causes prolongation of atrial refractoriness which contributes to the efficacy of the drug. Besides, it exerts frequency- and voltage-dependent sodium channels block, including the INaL, causing significant effect on the intra-atrial conduction particularly at fast rates.

In the amiodarone pretreated group IV, the resting heart rate did not differ significantly from those of the control group I and vernakalant treated group III. The effects of amiodarone on resting heart are evaluated in different studies. [Mason, 1987] stated that amiodarone decreases sinus rate about 15 to 20% and attributed this effect to its ability to inhibit intracellular conversion of thyroxin T4 to T3. [Djandjighian et al, 2000] also observed that amiodarone significantly and dose-dependently lowered the resting heart rate in animals and reduced the exercise-induced tachycardia which is probably due to its calcium channel and β-adrenocceptor blocking effects. These changes should not require discontinuation of amiodarone as they are evidence of its pharmacological action. [Arrendono, et al 1986]

In group IV, the mean heart rate decreased from T4 up to T23 with a percentage of reduction 17.5%, on comparison with that of the control group I, 38%. The difference in heart rate reduction in both groups, I and IV, was statistically significant. The antagonistic effect of amiodarone to bradycardia induced by reperfusion may be explained by its vasodilator effect [Zipese, et al 1984] and it was explained by [Patel et al, 2009] that amiodarone acts as a multichannel blocker by inhibiting a wide range of ion channels including IKs, IKr, IKur, IK-Ach, ICaL, INa+

The antagonistic effects of both vernakalant and amiodarone on reperfusion induced bradycardia were comparable with no statistically significant difference.

Coronary reperfusion (group II) resulted in changes in ST segment and T-wave inversion. There was an elevation of S-T segment in one animal, 10%, and a depression in another animal, 10%. after T5 then the percentages of animals showing elevation and those showing depression increased significantly to reach 40% for each after T10. From T12 and up to T22 there were also comparable ST segment elevation and depression with more tendencies to elevation.

It is contrary to that stated by [Heper et al, 2008] that successful reperfusion causes normalization or more than 50% regression of S-T segment elevation, T-wave inversion or any other dysrhythmias observed by electrocardiograph, S-T segment return is explained by rapid normalization of myocardial cell membrane potentials in the ischemic area as myocardial cells are capable of normalizing their membrane potential immediately as oxygen become available.

Treatment of the animals in group III with vernakalant increased insignificantly the percentages of animals showing elevated ST-segment compared with that in control group I. Vernakalant decreased significantly the percentages of animals showing ST-segment depression. In accordance with the observed results in this work, vernakalant could produce a dose-dependent reduction in ST-segment depression induced by exercise in experimental animals, suggesting that vernakalant's beneficial mechanism of action is due to an improvement in regional coronary blood flow in areas of myocardial ischemia mainly for non-transmural, subendocardial ischemia, it was stated by [Roy et al, 2004] that
in vivo human electrophysiology study and the CRAFT trial did not find a significant change in QRS or heart rate-corrected QT interval (QTc) by the infusion of vernakalant. In contrast, pivotal trials (ACT I, II, and III) showed that vernakalant increases the QRS and QTc intervals between 5 minutes and 2 hours after the start of infusion [Pratt, et al 2010]

Treatment of the experimental animals in group IV with amiodarone, abolished S-T segment elevation completely with a minor percentage of depressed S-T segment, remaining in only 10%-20%. Similar results were observed in the experimental animals by [Lindenmeyer et al, 1984]

Based on aforementioned results, it could be concluded that amiodarone is slightly more effective than vernakalant in correction of both elevated, transmural ischemia, and depressed S-T segment and non-transmural ischemia.

There were no significant changes in the regularity of the heart rate in the control group I up to T4. The dysrhythmias began from the T5 in 20% of animals and increased gradually, 30%, after T6 to 90% after T8 and at T9, 100%. These results were compatible to that stated by [Murdock et a. 1980] that the incidence of reperfusion-induced ventricular fibrillation increased when occlusion periods were lengthened from 5 minutes to 20 or 30 minutes and decreased when reperfusion was delayed beyond 30 to 60 minutes. Also, reperfusion-induced fibrillation tended to occur more often when severe arrhythmias developed during occlusion. It was also stated by [Casio et al, 2001] that changes in extracellular potassium (K) has been shown to fluctuate with coronary occlusion and reperfusion and that is also related to alterations in conduction that cause arrhythmias.

In the vernakalant treated group, III, the regularity of the heart beats was maintained up to T 23. Cardiac dysrhythmia did not develop in 90% of the rats and only 10% developed ventricular tachycardia with high doses, at T22 and T23 for 10 minutes. The anti-dysrhythmic action of vernakalant could be attributed to its atrial-selective ion-channel blocking properties that has recently been introduced for the acute management of cardiac dysrhythmias. [Dobrev & Nattel, 2010] Vernakalant inhibits atrial-selective K currents, including the ultra-rapidly activating delayed rectifier K current (I_{Kr}) and acetylcholine-activated inward rectifier K current (I_{Kach}), and causes rate-dependent atrial-preferential Na channel block, with only a small inhibitory effect on the rapidly activating delayed rectifier K current (I_{Kr}) in the ventricle. [Fedida, et al 2005]

Treatment of animals with amiodarone, Group IV, resulted in prevention of development of all type of dysrhythmias (100%) up to T23. The antidualrhythmic effect of amiodarone could be attributed to its due non-competitive alpha and beta adrenergic inhibition, class II activity, in addition, amiodarone blocks sodium channels, class I activity, moreover, it has a weak calcium channel blocking effect, class IV activity. [Gill, et al 1992]

Conclusion

Vernakalant showed a powerful antidualrhythmic action against ischemic-reperfusion cardiac dysrhythmias in experimental animals, comparable to that exerted by amiodarone with less recorded adverse drug effects causing beneficial properties of vernakalant against different types of cardiac dysrhythmias.

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Evaluating the Value of Intraperitoneal Ceftazidime Prior to Colonoscopy in Reducing Peritonitis in End Stage Renal Disease Patients on Peritoneal Dialysis

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Abstract

The biggest burden in peritoneal dialysis is still peritonitis which increases the rate of mortality and hospitalization. The aim of our research was to address one of the ISPD (international society of peritoneal dialysis) guidelines 2016 which advocate the use of prophylactic antibiotic in peritoneal dialysis patients before going to colonoscopy, but this recommendation is class C which means a weak one. Our aim was to look at the effect of giving intraperitoneal ceftazidime before the procedure of colonoscopy in reducing the possible risk of peritonitis.

Patients and methods: Over a period of 2 years and 6 months, from January 2016 we managed to enroll 120 patients out of 163 whom we performed 120 colonoscopies. Patients were randomized for Ceftazidime use by 1:1 method, ending up with 60 patients in group A who received the drug and 60 patients in group B who did not receive the drug.

Results: peritonitis occurred within 48 hours following the procedure. It was documented in 4 (6.7%) and 5 (8.3%) patients in groups 1 and 2 respectively (p =0.3243); the causative organisms were mainly gram-negative bacteria.

Conclusion: It appeared that giving intraperitoneal Ceftazidime prior to colonoscopy did not offer greater benefits in reducing the risk of peritonitis when compared with the group who did not receive it.

Keywords: Peritoneal dialysis, peritonitis, colonoscopy, ESRD, colon cancer, ceftazidime.

Introduction

The expansion of peritoneal dialysis uses in the late years as an option for renal replacement therapy (RRT) for end stage renal disease (ESRD) patients and the development of automated peritoneal dialysis (APD) have led to improved quality of life as well as increased survival among those patients. Maintaining patients on peritoneal dialysis for many years, however, has its own challenges that face nephrologists. These challenges based on the fact that most of ESRD patients are suffering from different comorbidities. Such challenges may require the need for other services namely cardiology, endocrinology, gastroenterology and others, each of which has its own diagnostic procedures that might harm patients if done without proper preparation. Colonoscopy is one of these procedures that may be required for both screening for and diagnosis of colon cancer as indicated. Colorectal cancer is still the third most prevalent cancer in USA general population. Although controversial, the overall incidence of cancer is reported to be higher in patients with ESRD than in the general population. An international study of cancer registries reported that, between the years 1980 to 1994, cancer occurred in 25,044 of 831,804 dialysis patients (compared with an expected number of 21,185), resulting in an overall standardized cancer incidence of 1.18. There are, however, no reported data concerning the prevalence of the disease amongst Saudi ESRD patients who are subjected to dialysis. Variable factors may influence the prevalence of colorectal lesions in this population in particularly diabetes, type and length on dialysis, statin use, immunosuppressive drugs and obesity. The current recommendations for colonoscopy screening in ESRD patients before renal transplantation are the same as those for the general population as detecting colorectal cancer may exclude patients from the transplant list for at least five years after clinical remission. The fear of developing peritonitis after colonoscopy is unjustified as few cases have been reported in the literature on post colonoscopy peritonitis in PD
patients (Reference 19-23). A retrospective study (Reference 24) found that the risk of peritonitis after colonoscopy without antibiotic prophylaxis was 6.3%; colonic biopsy or polypectomy did not appear to further increase the risk and no peritonitis was observed in patients that received prophylactic antibiotics although the difference was not statistically significant. Few cases have been reported on the incidence of peritonitis following colonoscopy in CAPD patients. Those reports claimed that instrumental diagnostic procedures such as colonoscopy may play a significant role in the development of gram-negative peritonitis in CAPD patients (References 25, 26). Similar results were reported by Yip et al in 2007 (Reference 27). All reported cases about peritonitis following colonoscopy were on CAPD and there were no case reports in APD patients. The recent guidelines of the International Society of Peritoneal Dialysis (ISPD) showed evidence 2-C favoring the use of prophylactic antibiotics prior to colonoscopy; however there have been no controlled randomized studies to support these recommendations. In view of these challenges, our study aimed at investigating the need of prophylactic antibiotics prior to colonoscopy in APD patients undergoing this procedure.

Patients and methods

Between January 2016 throughout June 2018, 120 patients out of 163 were included in this study. Patients were randomized (1:1) into two groups; Group 1: 60 patients on APD with prophylactic antibiotic therapy before the flexible colonoscopy, Group 2: 60 patients on APD without prophylactic antibiotics (Table-1). Exclusion criteria were: history of colonic or rectal resection, neurologic deficit, pregnancy, ongoing sepsis, valvular or chronic heart disease, urinary tract infections, chronic liver disease, exit-site or tunnel infections, pneumonia or pulmonary tuberculosis, peritonitis or history of peritonitis for the last one year and unwillingness to give informed consent (Figure-1). All flexible colonoscopy examinations were performed by trained gastroenterology consultants. All Staff in the endoscopy unit were aware of the potential hazard of cross-infection and assiduous mechanical cleaning followed by disinfection was done. The following parameters: age, gender, duration on dialysis, diabetic state, use of antibiotics before the procedure, and indications for and findings of colonoscopy were studied. APD peritonitis episodes occurring within 1 week after colonoscopy, culture results and outcomes of peritonitis were recorded. At our center, the colonoscopy bowel preparation protocol included a low residue diet 2 day before the examination and patients are instructed to take a fluid diet the day before the procedure. Oral electrolyte lavage solutions or aqueous sodium phosphate solution were used as laxative for bowel preparation. Peritoneal dialysis effluent (PDE) was drained and the patient’s abdomen was kept empty before the procedure. Prophylactic antibiotics were given for prevention of peritonitis if needed according to the 2010 ISPD guidelines (17). Prophylactic antibiotics for APD peritonitis prevention were not routine at our center. Peritonitis was diagnosed when abdominal pain and cloudy fluid occurred with or without fever, and when peritoneal fluid white blood cell (WBC) count was >100/mm3, with >50% neutrophils. Episodes with peritoneal eosinophilia but negative bacterial culture were excluded. The PDE was sent for hematological and microbiological examination when patients complained of abdominal pain or if the PDE was turbid. For the microbiological tests, 50 mL peritoneal fluid was centrifuged at 5000g for 15 minutes. The deposit was inoculated on 5% sheep blood agar, MacConkey agar, and Sabouraud agar and incubated aerobically at 35°C for up to 72 hours. All isolates were identified by standard biochemical methods and the identity of the isolates was confirmed using the Vitek Automicrobial System (bioMerieux, Vitek, Hazelwood, Missouri, USA). Antimicrobial susceptibility was tested by the Kirby–Bauer disk diffusion method and results interpreted according to the National Committee for Clinical Laboratory Standards criteria. Reappearance of signs of infection with the same organism(s) isolated in the dialysate within two weeks after the completion of antibiotic treatment was classified as relapse, and not as a new episode.

All Patients were on automated peritoneal dialysis (APD) and their dialytic prescription consisted of 1.36% and 2.27% glucose-based solutions Dianeal® over 9-10 hours night dwell and 7.5% icodextrin (Extraneal®, Baxter Castlebar, Ireland) 2 liters as the last fill for the day dwell. Total daily PD volume ranged between 10-12 liters with a fill volume ranging between 2.0-2.5 liters/cycle.
Colonoscopy procedure

In the procedure room, all patients were given supplemental oxygen (4 L/min) through a nasal cannula, and a 3-lead electrocardiogram, pulse oximetry, and blood pressure were monitored. Only the anesthesiologist certified in advanced life support and who completed a structured training program were permitted to administer propofol under the guidance of the endoscopist. The anesthesiologist who administered the sedative medications and physicians were present for the entire period of sedation and examination. The anesthesiologist attempted to achieve a level of sedation that allowed the patient to tolerate the procedure with minimal to mild pain while maintaining adequate cardiopulmonary function. Propofol induction of sedation was begun with an initial 40-mg bolus (20–30-mg for elderly and smaller patients at the discretion of the endoscopist and anesthesiologist) administered intravenously followed by titration with 10–20-mg boluses. After an initial bolus infusion of propofol, the patient was observed for 30–60 seconds before deciding to administer the next bolus. Fentanyl was administered intravenously in 12.5- or 25-g boluses and midazolam as 0.5–1.0-mg boluses. Additional medication was titrated at 1–3-minute intervals to achieve or maintain the desired level of sedation. An endoscopy technician was available to assist the Colonoscopy with technical maneuvers. This staffing pattern has been used in our endoscopy suite for all sedated procedures for several years and was not changed for the study. The following time points were recorded: initiation of sedation, full sedation (when the nurse and endoscopist mutually agreed the patient was sedated sufficiently to begin the procedure), colonoscope insertion, intubation of the cecum, and colonoscope removal from the anus. Interventional procedures like polypectomy were performed when indicated with disposable polypectomy snare G-Flex. Post polypectomy bleeding (if any) was managed by epinephrine injection, hemoclip and heat probe. Biopsies were taken when indicated by disposable biopsy forceps (Endow by Olympus). After the procedure, both the physician and the nurse completed a questionnaire that assessed the patient’s level of sedation, pain, and ability to cooperate. Any complications (decline in oxygen saturation to less than 85%, heart rate less than 50 beats per minute, blood pressure less than 90/50 mm Hg, or need for mechanical ventilation) were recorded.

Prophylactic antibiotic therapy

Antibiotic prophylaxis in our center consisted of first-line antibiotic regimen for APD peritonitis was first- or second-generation cephalosporin plus an aminoglycoside, either tobramycin or netilmicin. Cefazolin combined with ceftazidime was also used as alternative.

Peritonitis therapy

Peritonitis episodes were treated with our center’s standard antibiotic protocol, which has been changed systemically over time. The first-line antibiotic regimen for APD peritonitis was first- or second-generation cephalosporin plus gentamicin (loading dose 60 mg i.v. + 4-5 mg/L intraperitoneal). Cefazolin or cefoxitin (2 g i.v. + 50 mg/L intraperitoneal) combined with ceftazidime (2 g i.v. + 1 g intraperitoneal) was also used in our PD unit since the year 2010 according to the ISPD peritonitis guidelines (17). Vancomycin was used as a second-line therapy for primary nonresponding patients. Antibiotic regimens for individual patients were modified when culture results became available. Treatment usually lasted for either 2 weeks or at least 7 more days after normalization of the effluent WBC count, whichever was longer. Requirement of cessation of peritoneal dialysis, temporarily or permanently, and death during peritonitis, were defined as treatment failure. Heparin administration (500-1000 IU/L of dialysis fluid) and exchange of tubing was performed routinely in all cases of peritonitis. The indications for catheter removal included peritonitis caused by Pseudomonas species, peritonitis caused by fungi, cases with prolonged course or multiple recurrences, and episodes with suspected bowel perforation.

Statistical methods

Continuous variables are expressed as mean + SD and categorical variables are expressed as percentage. Non- parametric Spearman Rank test was used for continuous variables correlation and Mann-Whitney test used for comparison of two groups. P values were not adjusted for multiple testing.
and therefore should be considered descriptive. Variables with significant univariate associations were candidates for multivariate analysis. Univariate and multivariate analysis was used to study the relationship of age, sex, diabetes mellitus, time on APD, hemoglobin and albumin levels and prophylactic antibiotic use with post-colonoscopy peritonitis. The statistical analyses were limited to data regarding only the first episode of peritonitis, unless otherwise noted. Statistical significance was accepted at $p < 0.05$. The statistical analysis was performed using SPSS for Windows version 20 (IBM Inc. New York, USA).

Results

In a total of 163 APD patients included during the study period of 2 years and 6 months, 120 colonoscopies were performed in 120 APD patients. Mean age was 58.6 ± 10.1 years and duration of dialysis was 31.3 ± 8.6 months; 49 (40.8%) patients were diabetics. The 120 APD patients included in the study were randomized into two groups; group-1 (60 patients) who received IP cefazidime prophylaxis prior to colonoscopy and group-2 (60 patients) who had colonoscopy without antibiotic prophylaxis. Randomization was 1:1. Demographic characteristics of patients are summarized in table-1. The two groups were age and sex matching. Diabetes mellitus was present in 43.3% and 38.3% and hypertension in 85.0% and 81.7% in the two groups respectively ($p=0.3217$ & 0.3340). Mean duration of diabetes mellitus and the duration on APD was 18.6 + 11.7 years and 19.5 + 9.3 years, 31.3 + 10.7 months and 30.6 ± 12.2 months in groups 1 and 2 respectively ($p = 0.3937$ & 0.3821). The difference in overall fasting blood sugar (FBS) and hemoglobin A1-C (Hgb A1-C) was not statistically significant between the two groups. At the time of colonoscopy, the mean blood urea nitrogen (BUN), serum creatinine and renal creatinine clearance were 48.19 + 8.53 mg/dl and 46.32 + 9.84 mg/dl; 7.38 + 2.47 mg/dl and 8.13 + 2.87 mg/dl; 7.1 + 2.1 and 6.8 + 2.2 ml/min in groups 1 and 2 respectively with no statistical significance (table-1). Mean hemoglobin level, serum potassium (K+) and serum albumin were similar in both groups at the time of the procedure (table-1). Indications for and findings of colonoscopy are summarized in table-2 and figure-2. Of all colonoscopies 59.2% showed normal findings, 19.1% with colonic polyps at different sites, 10.8% with angiodysplastic-like lesions, 7.5% with colonic ulcer (s), 3.3% with diverticulae without diverticulitis and 1.7% had transverse colon stricture which was managed with stent insertion. Inflammatory bowel disease in the five patients was inactive for more than one year. Findings at colonoscopy are shown in figure-2. All Post-colonoscopy peritonitis occurred within 48 hours following the procedure. It was documented in 4 (6.7%) and 5 (8.3%) patients in groups 1 and 2 respectively ($p =0.3243$); the causative organisms were mainly gram-negative bacteria (5 out of 9 cases were gram negative bacteria, one with gram positive organisms, two negative culture and one with Candida albicans) (table-3). Peritonitis episodes were not documented in any patient with diverticulosis or biopsied colonic polyps. All peritonitis cases resolved with treatment and one patient from group 1 and 1 from group 2 required catheter removal because of fungal peritonitis in the former and refractory peritonitis in the later. Complications other than peritonitis were 0.0% in both groups. Different variables were analyzed to demonstrate its correlation with peritonitis episodes (Table-4). No significant difference in serum BUN or serum creatinine was observed between those who developed peritonitis and those who did not in the two groups. By multiple logistic regression analysis, the presence of diabetes mellitus was the only independent variable that entered into the best predictive equation over the development of enteric peritonitis (log likelihood ratio = -25.072, odds ratio = 17; 95% CI odds ratio: 2 - 151).
**Table 1.** Demographic characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 60)</th>
<th>Group B (n = 60)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean + SD</td>
<td>59 + 10.5</td>
<td>57 + 12.3</td>
<td>0.2412</td>
</tr>
<tr>
<td>Female/Male (female %)</td>
<td>23/60 (38.3)</td>
<td>21/60 (35.0)</td>
<td>0.3210</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>23.3</td>
<td>26.7</td>
<td>0.3062</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>51 (85.0)</td>
<td>49 (81.76)</td>
<td>0.2230</td>
</tr>
<tr>
<td>BMI at beginning, mean + SD</td>
<td>28.3 + 4.0</td>
<td>29.3 + 3.8</td>
<td>0.3020</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>26 (43.3)</td>
<td>23 (38.3)</td>
<td>0.3868</td>
</tr>
<tr>
<td>Duration of diabetes, (years), mean + SD</td>
<td>18.6 + 11.7</td>
<td>19.5 + 9.3</td>
<td>0.2937</td>
</tr>
<tr>
<td>Duration on APD, months (mean + SD)</td>
<td>31.3 + 10.7</td>
<td>30.6 + 12.2</td>
<td>0.3891</td>
</tr>
<tr>
<td>Overall FBS in diabetics, mmol/L (mean + SD)</td>
<td>8.6 + 1.2</td>
<td>8.4 + 1.8</td>
<td>0.2001</td>
</tr>
<tr>
<td>Overall Hgb A1C % in diabetics (mean + SD)</td>
<td>7.1% + 0.7</td>
<td>6.9 + 0.8</td>
<td>0.3773</td>
</tr>
<tr>
<td>Hgb at colonoscopy, gm/dl (mean + SD)</td>
<td>10.12 ± 2.25</td>
<td>10.32 ± 2.74</td>
<td>0.2434</td>
</tr>
<tr>
<td>BUN at colonoscopy, mg/dl (mean + SD)</td>
<td>48.19 + 8.53</td>
<td>46.32 + 9.84</td>
<td>0.2862</td>
</tr>
<tr>
<td>Serum Cr. at colonoscopy, mg/dl (mean + SD)</td>
<td>7.38 + 2.55</td>
<td>8.13 + 1.87</td>
<td>0.4051</td>
</tr>
<tr>
<td>Serum K+ (mEq/L)</td>
<td>3.8 + 1.9</td>
<td>3.9 + 2.1</td>
<td>0.5100</td>
</tr>
<tr>
<td>Serum albumin (gm/l)</td>
<td>3.8 + 2.0</td>
<td>3.7 + 1.8</td>
<td>0.4224</td>
</tr>
<tr>
<td>Renal Cr Cl. ml/m (mean + SD)</td>
<td>7.1 + 2.1</td>
<td>6.8 + 2.2</td>
<td>0.3482</td>
</tr>
</tbody>
</table>


**Table 2.** Indications for and findings of colonoscopy

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Indication</th>
<th>Findings (number)</th>
<th>Action (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 (18.3)</td>
<td>Screening for colonic Cancer</td>
<td>Normal (15)</td>
<td>None (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transverse and descending colon polyps (7)</td>
<td>Biopsies and removal (7)</td>
</tr>
<tr>
<td>18 (15.0)</td>
<td>Investigation for iron deficiency anemia</td>
<td>Normal (15)</td>
<td>None (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiodysplastic like lesions (3)</td>
<td>Biopsies &amp; bleeding protocol (3)</td>
</tr>
<tr>
<td>16 (13.3)</td>
<td>Altered bowel habits (chronic diarrhea or chronic constipation)</td>
<td>Normal (9)</td>
<td>None (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diverticulae (4) Transverse colon polyps (3)</td>
<td>None (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None (4)</td>
<td>Biopsies and removal (3)</td>
</tr>
<tr>
<td>15 (12.5)</td>
<td>Positive fecal occult blood testing without overt rectal bleeding</td>
<td>Normal (6)</td>
<td>None (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiodysplastic-like lesions (6) Descending colon polyp (3)</td>
<td>Biopsies &amp; bleeding protocol (6) Biopsies and removal (3)</td>
</tr>
<tr>
<td>13 (10.8)</td>
<td>Overt rectal bleeding</td>
<td>Normal (3)</td>
<td>None (3)</td>
</tr>
<tr>
<td>Patient’s No#</td>
<td>Group 1 (4 cases) Microorganisms</td>
<td>Outcome</td>
<td>Patient’s No#</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------</td>
<td>-----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>12</td>
<td>E. coli + Enterobacter</td>
<td>Treated</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>Candida albicans</td>
<td>PD catheter removed</td>
<td>22</td>
</tr>
<tr>
<td>33</td>
<td>Klebsiella</td>
<td>Treated</td>
<td>29</td>
</tr>
<tr>
<td>35</td>
<td>S. aureus</td>
<td>Treated</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>59</td>
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</tbody>
</table>

Table 3. Microorganisms responsible for peritonitis
Table 4. Comparison of characteristics of patients with and without peritonitis after colonoscopy

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Peritonitis</th>
<th>Group 2 Peritonitis</th>
<th>p</th>
<th>Group 2 Peritonitis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>4 (6.7) 56 (93.3)</td>
<td>5 (8.3) 55 (91.7)</td>
<td>0.3243</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>58.0 + 10.3 57.0 + 12.3</td>
<td>58.1 + 11.1 58.2 + 10.7</td>
<td>0.4642</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>4/4 (100) 22/56 (39.3)</td>
<td>5/5 (100) 18/55 (32.7)</td>
<td>0.0312</td>
<td></td>
<td>0.0336</td>
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<tr>
<td>Duration on APD, month, (mean)</td>
<td>31.1 + 9.5 30.7 + 10.4</td>
<td>29.7 + 10.2 30.1 + 9.4</td>
<td>0.3292</td>
<td></td>
<td>0.3844</td>
</tr>
<tr>
<td>BUN, mg/dl (mean)</td>
<td>47.6 + 9.7 48.3 + 11.2</td>
<td>46.0 +7.8 45.8 + 10.1</td>
<td>0.4004</td>
<td></td>
<td>0.4005</td>
</tr>
<tr>
<td>Creatinine, mg/dl (mean)</td>
<td>7.2 + 2.2 7.1 + 2.4</td>
<td>7.8 + 2.7 8.0 + 2.2</td>
<td>0.4137</td>
<td></td>
<td>0.3334</td>
</tr>
<tr>
<td>Hemoglobin, gm/dl (mean)</td>
<td>9.8 + 2.4 10.1 + 2.2</td>
<td>10.1 + 2.7 10.3 + 1.9</td>
<td>0.3146</td>
<td></td>
<td>0.4113</td>
</tr>
<tr>
<td>Serum K+, mEq/l (mean)</td>
<td>3.8 + 1.1 3.7 + 1.8</td>
<td>3.7 + 2.0 3.7 + 2.1</td>
<td>0.4480</td>
<td></td>
<td>0.5131</td>
</tr>
<tr>
<td>Serum albumin, gm/dl (mean)</td>
<td>3.7 + 2.2 3.8 + 1.2</td>
<td>3.6 + 1.9 3.7 + 2.2</td>
<td>0.3433</td>
<td></td>
<td>0.5010</td>
</tr>
</tbody>
</table>

APD: automated peritoneal dialysis, BUN: blood urea nitrogen, K+: potassium
Figure 1. Consort diagram demonstrating study design and patients' progress

CHD: chronic or valvular heart disease, UTI: urinary tract infection, CLD: chronic liver disease, ESI: exit-site infection, TI: tunnel infection, peritonitis: ongoing or previous.

Figure-2. Colonoscopy findings in the study population
**Discussion**

Peritonitis in PD patients after colonoscopy is a known but infrequent complication. A retrospective study from Hong Kong revealed an average risk of peritonitis after colonoscopy of 6.3% in 77 CAPD patients after 97 endoscopic procedures. Colonic biopsy or other interventions such as polypectomies apparently did not increase the risk of peritonitis (19-21). The source of contamination in those cases not associated with catheter exit-site or tunnel infections is thought to be transmural (1, 19). Microorganisms may gain access to the peritoneum from the intestinal lumen or through genital organs (22, 23). Diagnostic instrumental procedures, such as colonoscopy, have been implicated in the development of these peritonitis episodes (14, 15). Post colonoscopy peritonitis in patients undergoing PD is thought to result from translocation of microorganisms across the bowel wall (24) and it has been alleged that gastrointestinal endoscopic procedures in those patients can lead to peritonitis (25). However, in many cases there is no evidence that links peritonitis to colonoscopy as a risk factor (21, 22). The recommendations concerned with colonoscopy in PD patients are not based on randomized controlled trials because such studies in PD patients are limited. Where there is no definitive evidence; but the group feels there is sufficient experience to suggest a certain approach, this is indicated as “opinion” based. The recommendations are not meant to be implemented in every situation but are recommendations only. Each center should examine its own pattern of infection, causative organisms, and sensitivities and adapt the protocols as necessary for local conditions (20). Contrary to Yip et al (11) who, in a selected cohort, suggested that diverticulosis may be a risk factor for the development of enteric peritonitis, we did not encounter such complication in our patients. Moreover, colonic diverticulosis did not appear to affect the outcome of colonoscopy in our study. Supporting our findings was the report by Toda et al. (26) who studied 317 PD-candidate patients over approximately 4 years and concluded that asymptomatic diverticulosis identified by computed tomography was not a risk factor for enteric peritonitis in their study population. In addition, colon biopsy or polypectomy did not appear to further increase the risk of peritonitis in our cohort. A retrospective study by Yip et al. (27) found that the risk of peritonitis after colonoscopy without antibiotic prophylaxis was 6.3%. The authors however, indicated that it lacks statistical significance. Interestingly, the International Society for Peritoneal Dialysis recommended antibiotic prophylaxis before any procedure involving the abdomen or pelvis, including colonoscopy (16). Again, it is important to notice that these recommendations were based only on observational studies and case reports. The 2005 and the 2016 ISPD guidelines suggested empirical 1- gram ampicillin or aminglycoside with or without metronidazole before colonoscopy (16, 28). These guidelines recommend antibiotic prophylaxis for CAPD patients undergoing colonoscopy with polypectomy; however, there has been little literature to support these recommendations. Studies on these guidelines are rare, and randomized controlled trials to support this recommendation are lacking. Moreover, these new guidelines clearly stated that the optimal antibiotic regimen has not been determined by clinical studies yet (16). Contrary to the suggestions above, the American Society for Gastrointestinal Endoscopy and the British Society of Gastroenterology do not suggest prophylactic antibiotics before colonoscopy (29, 30). There exists a lack of consensus on this issue. There have been few case reports in the literature on peritonitis following colonoscopy in peritoneal dialysis patients (6, 7, 14-16). These reports suggested that instrumental procedures such as colonoscopy may precipitate gram-negative peritonitis in PD patients. On the other hand, some literature reported bacterial peritonitis following endoscopic polypectomy in peritoneal dialysis patients despite antibiotics prophylaxis (10). So far there are no strong data demonstrating a causal association between endoscopic procedures and bacteremia or that antibiotic prophylaxis prior to endoscopic procedures protects against bacteremia. Much of the existing data reflects estimated risk associated with conventional endoscopic techniques. There are no results available that confidently quantify bacteremia rates with newer endoscopic procedures such as per oral endoscopic myotomy, endoscopic submucosal dissection, flexible colonoscopy or polypectomy (11). Use of a single IP antibiotic prophylaxis was encouraged by many authors based on pharmacokinetic (PK) evidences. In the study of the PK of IP cefazolin and ceftazidime, Elwell, et al. reported serum cefazolin and ceftazidime levels that exceeded the minimum inhibitory concentrations for susceptible organisms (8 mg/L) throughout the 20 hours study period. Predictive equations suggested that 1000 mg IP of cefazolin or ceftazidime every 24 hours would produce average steady-state trough serum cefazolin and ceftazidime concentrations of 70 +/- 52 mg/L.
and 17 +/− 7 mg/L, respectively. In another study, Tobudic, et al. (28) reported that the maximum serum concentrations after intravenous and IP administration of other antibiotics were comparable. Ratios of IP to systemic exposure indicated good systemic exposure after intraperitoneal application but limited penetration of the antibiotic into the peritoneal fluid after the intravenous dose. Similar results were reported by Weisholzer, et al. and Low, et al. (29). In 2006, A well designed prospective study of PK of cefepime by Elwell, et al. suggested that most APD and CAPD patients would achieve adequate serum cefepime concentrations if infused with a standard dose of 1000 mg given IP (9). It is becoming an accepted policy to use IP instead of IV antibiotics in PD patients when needed, as IP applications of antibiotics achieves a higher target-site concentration, less gastrointestinal side effects and improved compliance. We studied APD patients with and without IP antibiotic prophylaxis before flexible colonoscopy. The difference in peritonitis episodes in our study between the two groups was not statistically significant (6.7% vs. 8.3%, p > 0.05). Interestingly, transient bacteremia occurs frequently during routine daily activity, often at rates exceeding those associated with endoscopic procedures. Brushing and flossing of teeth has been associated with rates of bacteremia of 20% to 68%, use of toothpicks with rates of 20% to 40%, and even activity that might be considered entirely physiologic, such as chewing food, with rates ranging from 7% to 51%. By multiple logistic regression analysis, the use of prophylactic antibiotics prior to colonoscopy was not a predictive variable for developing post-colonoscopy peritonitis in our study population. One patient from those who received prophylactic antibiotics had Candida species in peritoneal fluid culture. Although we could not prove the relation between antibiotic prophylaxis and the development of this un-expected growth, it is not unreasonable to speculate that antibiotic administration may have favored intestinal non-bacterial overgrowth (Candida in our case) and use of more than one antibiotic may make it even worse. Given the notorious possibility of resistant strains’ development and the relative rarity with which most PD patients undergo colonoscopy procedures, the frequency and risk of colonoscopy-related bacteremia, as we demonstrated in our study, is trivial compared with the frequency of bacteremia encountered with routine daily activity. This may provide a reasonable basis against routine administration of antibiotic prophylaxis prior to all endoscopic procedures. There are, however, some limitations in our study. First, this study was conducted in a single tertiary medical center, and endoscopy-associated complications may vary in different hospitals. Second, the study was conducted on a selected group of APD patients after applying strict exclusion criteria. Third, the study used a single antibiotic and may have underestimated the importance of combined antibiotic prophylaxis. Therefore, larger randomized trials are required to explore the necessity of antibiotic prophylaxis in the prevention of post-colonoscopy PD peritonitis. Nevertheless, our study has the strength of being the first prospective randomized study in this field.

Conclusion

There was no correlation between the risk of peritonitis and intraperitoneal prophylactic ceftazidime. Only old age, diabetes mellitus and low serum albumin appeared to be of significance. Neither polypectomy; partial or complete nor diverticulosis were associated with increased incidence of post-colonoscopy peritonitis. However, the study may have underestimated the importance of antibiotic prophylaxis. Therefore, larger prospective multicenter randomized trials are needed.

References
