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Safety in Surgery: Evaluation of Safety and Efficiency in Use of Aminoglycosides in Acute Appendicitis

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Abstract

Background: Aminoglycosides are used as empirical antibiotic treatment of intraabdominal infections which are caused by Gram negative bacteria and for which the treatment of choice is surgery. Aminoglycosides maintain good efficacy against these bacteria and reduce the need for prescribing fluoroquinolone, cephalosporin and carbapenem antibiotics which contribute to the development of resistant bacterial strains. In recent years, several clinical trials and international guidelines have advised against the use of aminoglycosides owing largely to doubts about their effectiveness and to the concern for their known nephrotoxicity and ototoxicity. **Aim:** In our study, we aimed to prove whether aminoglycosides are appropriate agents in the treatment of acute appendicitis. **Methods:** Retrospectively, patients with acute appendicitis we included in the trial. Demographic characteristics, comorbidities, clinical signs and symptoms, the type of antibiotic and surgical treatment were analyzed. The effect of independent variables on the occurrence of complications was calculated using Student's T-test and Fisher's precise test. The effect of aminoglycosides on the loss of kidney function was determined by means of a linear regression method. **Results:** 300 patients proved acute appendicitis were included in the study. Univariate statistical analysis showed that the risk factors for postoperative complications in treating acute appendicitis were: age over 76 years ($p < 0.001$), acute perforated appendicitis ($p = 0.03573$) and appendicitis with periappendiceal infection ($p = 0.01253$), the presence of cardiovascular ($p < 0.001$), pulmonary ($p = 0.00339$), and kidney ($p < 0.001$) diseases, and no an achieved ASA group of IV ($p < 0.001$). Treatment with aminoglycosides did not influence the occurrence of postoperative complications ($p = 0.3135$). Multivariate statistical analysis showed that aminoglycosides did not have a statistically significant effect on the decrease of glomeru-

lar filtration rate. **Conclusion:** Aminoglycoside antibiotics are a safe and effective treatment of acute appendicitis; our not published data are positive of AGs use in acute cholecystitis and left colon diverticulitis which requires surgery. If used for a limited time period, they do not increase the risk for kidney injury and remain a stable low level of all over complications.

Keywords

IAI (Intraabdominal Infections), Aminoglycosides, Acute Appendicitis, Safety Use and Efficiency

1. Introduction

Safety use of antibiotics in human medicine and surgery is important to prevent treatment complications and from the point of view of MDR (multidrug resistance). Due to the increasing prevalence of MDR gram-negative infections in surgical patients caused by *Enterobacteriaceae, Pseudomonas* spp. *and Acinetobacter* spp. Aminoglycosides (AGs) represents the critical option of use; AGs are identified being critically important for treatment of enterococcal endocarditis, MDR Gram-negative bacteria (especially *Enterobacteriaceae* and *Pseudomonas* spp.), Gram-positive bacteria such as enterococci and mycobacteria and MDR tuberculosis. AGs have favorable chemical and pharmacokinetic properties and are clinically useful. Improved understanding of the mechanisms of toxicity and efficacy favored the implementation of AGs based on optimization of dosing regimens that consequently represent improved safety and efficacy.

Infections within the abdominal cavity (intra-abdominal infections, IAIs) are the consequence of inflammation and/or disruption of the gastrointestinal tract and less commonly, they can arise from the gynecologic or urinary tract, also. Combined infections are present more frequently in cases of chronic renal disease, malignancies and impaired immunity (diabetes mellitus, immune suppressant medications acquired immune deficiency syndrome). Abdominal infections are usually polymicrobial and result in an intra-abdominal abscess or secondary peritonitis, which may be generalized or localized (phlegmon). A special origin of abdominal infections represents recurrent urinary tract infections (rUTI) and gynecological, mostly adnexal and pelvic abscess with polymicrobial flora.

IAIs are an important cause of morbidity and mortality. Management of IAIs require early clinical diagnosis, adequate source control, patient dictated appropriate antimicrobial therapy, infection risk factors detection and prompt resuscitation to optimize outcomes. Prognostic scoring systems for complicated IAIs are useful in clinical practice and are divided into: general organ failure severity (ICU) and peritonitis-specific (surgical) scores. The Sequential Organ Failure Assessment (SOFA) score is for the purpose to follow the evolving disease process in critically ill patients in ICU.

Treatment success is defined as adequate source control with a resolution of

sepsis, abdominal sepsis and clearance of all residual intra-abdominal infection. Antimicrobial therapy for patients with IAI needs to be timed to optimize management of the infection and to prevent secondary infections following source control. The duration of antimicrobial therapy in the patient with IAI needs to be specific. In critically ill patients we have to consider altered pharmacokinetic parameters that might result in underdosing and/or overdosing of anti-infective agents; dosing for source control IAIs have to be adapted to: the extremes of age, obese patients, renal or hepatic impairment.

2. Aim of the Study

To prove whether aminoglycosides are appropriate agents in the treatment of acute appendicitis a retrospective analysis of patients treated in the Department of Abdominal Surgery, University Medical Center Ljubljana, was performed.

3. Materials and Methods, Results

Patients with acute appendicitis we included; demographic characteristics, comorbidities, clinical signs, and symptoms, the type of antibiotic and surgical treatment was analyzed. 351 patients were analyses Patient characteristics of the whole sample are presented in Table 1.

Table 1. Acute appendicitis and aminoglycoside.

	aminoglycoside therapy (N = 319)	no aminoglycoside therapy (N = 96)	p value
Gender			0.130
female	148 (46.4%)	53 (55.2%)	
male	171 (53.6%)	43 (44.8%)	
Age group			0.108
15 - 25	77 (24.1%)	33 (34.4%)	
26 - 35	76 (23.8%)	26 (27.1%)	
36 - 45	65 (20.4%)	17 (17.7%)	
46 - 55	27 (8.5%)	8 (8.3%)	
55+	74 (23.2%)	12 (12.5%)	
BMI			0.453
Mean (SD)	26.04 (4.63)	24.98 (4.10)	
Median (Q1, Q3)	25.30 (22.95, 29.45)	24.55 (22.52, 27.70)	
Min - Max	17.60 - 37.20	18.20 - 32.80	
Cardiovascular disease			0.079
no	270 (84.6%)	88 (91.7%)	
yes	49 (15.4%)	8 (8.3%)	
Lung disease			0.968
no	306 (95.9%)	92 (95.8%)	
yes	13 (4.1%)	4 (4.2%)	

Continued

Kidney disease			0.583
no	318 (99.7%)	96 (100.0%)	
yes	1 (0.3%)	0 (0.0%)	
Neurological disease			0.200
no	317 (99.4%)	94 (97.9%)	
yes	2 (0.6%)	2 (2.1%)	
Immobility			0.200
no	317 (99.4%)	94 (97.9%)	
yes	2 (0.6%)	2 (2.1%)	
Cancer			0.437
no	317 (99.4%)	96 (100.0%)	
yes	2 (0.6%)	0 (0.0%)	
Diabetes type 2			0.096
no	310 (97.2%)	96 (100.0%)	
yes	9 (2.8%)	0 (0.0%)	
Other diseases			0.894
no	284 (89.0%)	85 (88.5%)	
yes	35 (11.0%)	11 (11.5%)	
ASA score			0.275
I	169 (53.8%)	58 (61.1%)	
II	118 (37.6%)	34 (35.8%)	
III	24 (7.6%)	3 (3.2%)	
IV	3 (1.0%)	0 (0.0%)	
Complications			0.561
no	268 (84.0%)	83 (86.5%)	
yes	51 (16.0%)	13 (13.5%)	

Sample description acute appendicitis (Figure 1). Univariate analysis was performed to present the effect of different independent variables on the occurrence of complications using Student's T-test and Fisher's precise test. The effect of aminoglycosides on the loss of kidney function was determined utilizing a linear regression method.

Diagnose comparison acute appendicitis (Table 2 and Table 3). The average (mean) aminoglycoside treatment duration was 3.04 days. Calculated p-value is <0.001. Among different observed parameters statistical significance was positive for BMI ($p = 0.047$), gender ($P = 0.047$), pulmonary disease ($p < 0.0039$) and cardiovascular disease ($p < 0.001$) and grade of IAI ($P = 0.01$). No ASA score and concomitant disease, cancer, kidney disease, arterial hypertension was statistically significant in diagnose comparison.

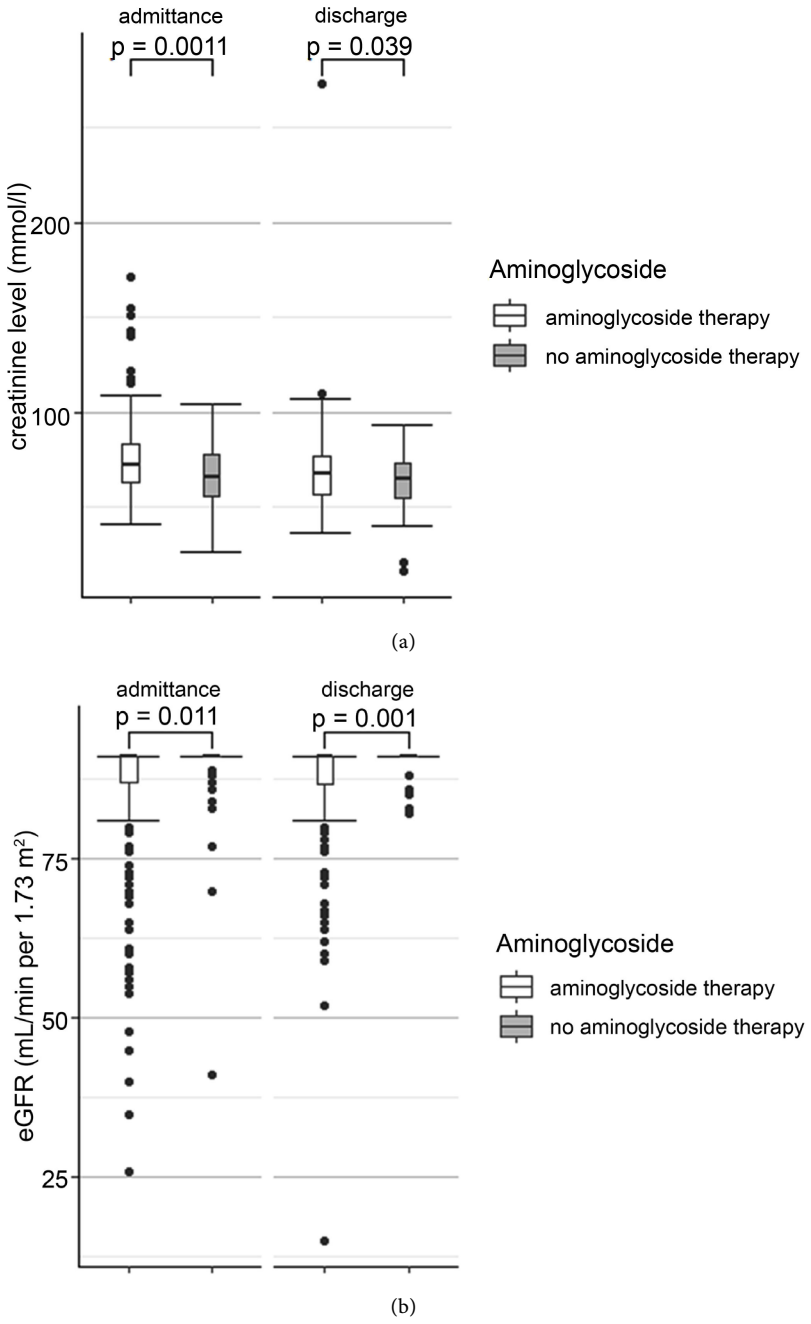

Figure 1. (a) and (b) Creatinine level (mmol/l) and glomerular filtration rate (eGFR mL/min per 1.73 m^2). Linear regression for calculation the impact of AGs to the rate complication. (a) Creatinine level and aminoglycoside; (b) eGFR (mL/min per 1.73 m^2) and aminoglycoside

Table 2. Comparison by complications—acute appendicitis.

	no (N = 351)	yes (N = 64)	p value
Gender			0.587
female	172 (49.0%)	29 (45.3%)	
male	179 (51.0%)	35 (54.7%)	

Continued

Age group			0.016
15 - 25	95 (27.1%)	15 (23.4%)	
26 - 35	90 (25.6%)	12 (18.8%)	
36 - 45	74 (21.1%)	8 (12.5%)	
46 - 55	24 (6.8%)	11 (17.2%)	
55+	68 (19.4%)	18 (28.1%)	
BMI			0.646
Mean (SD)	25.87 (4.52)	25.22 (4.64)	
Median (Q1, Q3)	25.40 (22.55, 29.20)	24.50 (21.90, 27.80)	
Min - Max	17.60 - 37.20	19.30 - 32.80	
Cardiovascular disease			0.271
no	300 (85.5%)	58 (90.6%)	
yes	51 (14.5%)	6 (9.4%)	
Lung disease			0.103
no	339 (96.6%)	59 (92.2%)	
yes	12 (3.4%)	5 (7.8%)	
Kidney disease			0.019
no	351 (100.0%)	63 (98.4%)	
yes	0 (0.0%)	1 (1.6%)	
Neurological disease			0.391
no	347 (98.9%)	64 (100.0%)	
yes	4 (1.1%)	0 (0.0%)	
Immobility			0.391
no	347 (98.9%)	64 (100.0%)	
yes	4 (1.1%)	0 (0.0%)	
Cancer			0.175
no	350 (99.7%)	63 (98.4%)	
yes	1 (0.3%)	1 (1.6%)	
Diabetes type 2			0.568
no	344 (98.0%)	62 (96.9%)	
yes	7 (2.0%)	2 (3.1%)	
Other diseases			0.968
no	312 (88.9%)	57 (89.1%)	
yes	39 (11.1%)	7 (10.9%)	
ASA score			< 0.001
I	202 (58.2%)	25 (40.3%)	
II	123 (35.4%)	29 (46.8%)	
III	22 (6.3%)	5 (8.1%)	

Continued

IV	0 (0.0%)	3 (4.8%)	
Aminoglycoside therapy			0.561
aminoglycoside therapy	268 (76.4%)	51 (79.7%)	
no aminoglycoside therapy	83 (23.6%)	13 (20.3%)	
Aminoglycoside therapy duration			<0.001
Mean (SD)	2.74 (1.74)	4.63 (2.35)	
Median (Q1, Q3)	2.00 (1.00, 4.00)	5.00 (3.00, 6.50)	
Min - Max	1.00 - 11.00	1.00 - 9.00	

Table 3. Diagnose comparison.

Gender	
female	201 (48.4%)
male	214 (51.6%)
Age group	
15 - 25	110 (26.5%)
26 - 35	102 (24.6%)
36 - 45	82 (19.8%)
46 - 55	35 (8.4%)
55+	86 (20.7%)
BMI	
Mean (SD)	25.79 (4.51)
Median (Q1, Q3)	25.20 (22.52, 29.10)
Min - Max	17.60 - 37.20
ASA score	
I	227 (55.5%)
II	152 (37.2%)
III	27 (6.6%)
IV	3 (0.7%)
Complications	
no	351 (84.6%)
yes	64 (15.4%)
Aminoglycoside therapy	
aminoglycoside therapy	319 (76.9%)
no aminoglycoside therapy	96 (23.1%)
Aminoglycoside therapy duration	
Mean (SD)	3.04 (1.97)
Median (Q1, Q3)	3.00 (1.00, 4.00)
Min - Max	1.00 - 11.00

The impact of variables on complication rate, acute appendicitis (Table 4). The impact of single variable on complication rate; the use of aminoglycoside to the complication rate (impaired kidney function) was presented with a linear regression model. Multiple variables were analyzed simultaneously to evaluate

Table 4. Different variables and acute appendicitis.

	aminoglycoside therapy (N = 319)	no aminoglycoside therapy (N = 96)	p value
Cardiovascular disease			0.079
no	270 (84.6%)	88 (91.7%)	
yes	49 (15.4%)	8 (8.3%)	
Lung disease			0.968
no	306 (95.9%)	92 (95.8%)	
yes	13 (4.1%)	4 (4.2%)	
Kidney disease			0.583
no	318 (99.7%)	96 (100.0%)	
yes	1 (0.3%)	0 (0.0%)	
Neurological disease			0.200
no	317 (99.4%)	94 (97.9%)	
yes	2 (0.6%)	2 (2.1%)	
Immobility			0.200
no	317 (99.4%)	94 (97.9%)	
yes	2 (0.6%)	2 (2.1%)	
Cancer			0.437
no	317 (99.4%)	96 (100.0%)	
yes	2 (0.6%)	0 (0.0%)	
Diabetes type 2			0.096
no	310 (97.2%)	96 (100.0%)	
yes	9 (2.8%)	0 (0.0%)	
Other diseases			0.894
no	284 (89.0%)	85 (88.5%)	
yes	35 (11.0%)	11 (11.5%)	
ASA score			0.275
I	169 (53.8%)	58 (61.1%)	
II	118 (37.6%)	34 (35.8%)	
III	24 (7.6%)	3 (3.2%)	
IV	3 (1.0%)	0 (0.0%)	
Complications			0.561
no	268 (84.0%)	83 (86.5%)	
yes	51 (16.0%)	13 (13.5%)	

the possible impact of aminoglycoside use on the incidence of complication rate in acute appendicitis and the impact on kidney function.

Two variables presented, neurological disease and ASA score were statistically significant to the incidence of complications. Standard parameters were used, creatinine and oGFR (ml/min per 1.73 m^2). Regression coefficient was calculated: oGFR = 9.76 × Neurological disease + 6.79 × ASA (R = 0.212) and calculated regression coefficient for calculation of the effect of aminoglycoside to kidney function OGFR = −5.41 + 4.56 × ASA (R = 0.205).

Based on the calculation-calculated regression coefficient strongly support our clinical experience that AGs are safe and effective for treatment acute appendicitis, presented and summarized in **Figure 1(a)** and **Figure 1(b)**: no impact of AGs use to oGFR and creatinine level.

Importantly, multivariate statistical analysis showed aminoglycosides did not have a statistically significant effect on the decrease of glomerular filtration rate taking in view limited time period treatment. AGs use is correlated with an importantly reduced rate of antimicrobial resistance (AMR) that have been of relevant clinical importance in treating complicated IAI.

4. Discussion and Conclusions

Management of intra-abdominal infection (IAI) is a daily practice; different population characteristics: aging of the population, the burden of chronic disease and increased prevalence of resistant bacteria and fungi in both the healthcare setting and the community highly suggest the implementation of guidelines in daily practice [1] [2] [3]. Source control and personalized approach are important to reduce the incidence of all over complications.

For effective treatment of IAIs with an acceptable low rate of complications an appropriate antimicrobial therapy should be started early in the disease course, an adequate diagnostic tool used and adequate source control implemented. Empirical antibiotic therapy is recommended to be introduced and followed by a different antibiotic scheme after sample identification. This should represent the daily practice to reduce the rate of abdominal sepsis and the consequences and the recommended management strategy. According to data described in the WISS study, around one-third of acute appendicitis cases are the complicated and inadequate source control is the leading course for abdominal sepsis [4]. Early recognitions of the disease and proper management strategy reduce the reported morbidity and mortality associated with acute appendicitis; of the important factors to contribute to morbidity and mortality are delays in a presentation by patients, delay in diagnosis by the clinician and misdiagnose in certain circumstances like obesity, pregnancy and cancer disease. The complications are clinically presented like perforation, appendiceal mass, local and/or diffuse peritonitis and gangrene. All clinical circumstances prolong hospital stay, increase the calculated rate of short- and long-term complication rate, increase the cost of treatment and reduce QL and increase invalidity.

The duration of antimicrobial therapy in the patient with IAI needs to be specific for each clinical condition. Insufficient timing of antimicrobial treatment is correlated to increased risk of unfavorable outcomes and long term complications and also the increased risk of AMR in local hospital environment. To reduce the incidence of resistant antimicrobials and treatment complications time-limited period is mandatory [1] [2] [3] [4] [5]. Our results strongly support the guidelines realized by the Surgical Infection Society (SIS) that in 2016 published the revised guidelines targeted to acute IAI and also based on comprehensive review of Sarteli *et al.* and the studies performed in WSES [3] [6] [7] [8] [11] [13]. Acute appendicitis, acute cholecystitis, and perforated diverticulitis were studied in WISS study with the next conclusions: patients with acute or gangrenous appendicitis in the absence of perforation, patients with acute or gangrenous cholecystitis in the absence of perforation, and patients with ischemic, non-perforated bowel need limited antimicrobial therapy to four days (96 h) in cases with adequate source control with strong, Grade 1A recommendation. Consequently, 5 - 7 days treatment period is needed in patients with source control not performed [1] [3] [4] [5].

Locally realized data on AMR released twice per year from authorized certified intra-hospital laboratory showed excellent bacterial sensitivity to AGs among *Enterobacteriaceae sp.* (all over 94% with exception of *K. pneumoniae* ESBL and *E. coli* ESBL, 51% and 64% sensitivity, respectively) and non-fermentative G-clinical isolates among them *P. aeruginosa* have stable sensitivity of 95%) dictate suggested source control regimens that have been implemented in the treatment protocol for acute appendicitis. Thus, our results do not support SIS recommendation on aminoglycoside-based regimens that do not support routine use for empiric therapy; to respect the data realized twice a year by responsible institutions and to maintain low AMR profile we propose AGs based regimens for treatment of acute appendicitis in the adult population and also for other IAI; personal data not published yet, showed same good profile of AGs use in acute cholecystitis and left colon diverticulitis [8] [9] [10]. This conclusion based on our data is supported also with NICE guidelines for treatment of diverticular disease published in 2019 and the paper of Slomkin and colleagues in 2010 [11] [12] [13] [14] [15]. Our results are in accordance to European Medicines Agency that support our results that limited time period aminoglycoside treatment for surgical IAI treatment is safe [11] [13] [14] [15]. European Medicines Agency classified AGs critically important antimicrobials (CIAs) but not included with the highest priority (CIAs) [11]. Besides, also, recommendations published lastly, increased prevalence of MDR Gram-negative infections (*Enterobacteriaceae*, *Pseudomonas* spp. and *Acinetobacter* spp.) identified AGs as critically important for the treatment of enterococcal endocarditis, multidrug-resistant Gram-negative bacteria (especially *Enterobacteriaceae* and *Pseudomonas* spp.) and multidrug-resistant tuberculosis). By the study of Kumar *et al.* early combination therapy with AGs has been associated with reduced mortality in septic shock [3] [4] [8] [9] [10] [11] [12]. Studies also confirmed lower toxicity in single day dose regimens, both

nephrotoxicity and ototoxicity. In the randomized, double-blind trial of different AGs of Rybak *et al.* The authors concluded that AGs administered once- or twice-daily used in shorter courses of therapy demonstrated a significantly lower incidence of nephrotoxicity with once-daily dosing8. Thus, this comes opposite to the old dogma AGs downplaying these drugs because of their lower efficacy and nephrotoxicity. Importantly, early survival benefit in patients with septic shock have revitalized their use from the point of view of increasing antimicrobial resistance that is the growing problem in human and animal daily practice treatment protocols [9] [12] [13]. Besides, it is important to implement all practices to prevent transmission of resistant *Enterobacteriaceae* from non-human sources to human with a high incidence; AGs are considered critical for the treatment of enterococcal endocarditis in a human and multidrug-resistant tuberculosis [9] [11] [12]. In conclusion, short-term and limited time period treatment of acute appendicitis in the study group was not correlated with the higher complication rate which refers to nephrotoxicity; strong statistical correlation also supports the idea that AGs use is safe and efficient to maintain good antimicrobial resistance profile, confirmed with certified in-hospital data. No higher rate of other surgical and non-surgical complications was observed. Based on literature data and results from a personal non-published study on acute cholecystitis and left colon diverticulitis we can transfer our conclusions also to the treatment of other IAIs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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