Acute kidney injury and single-dose administration of aminoglycoside in the Emergency Department: a comparison through propensity score matching

Articoli Originali

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ABSTRACT

Purpose: According to the Surviving Sepsis Campaign, aminoglycosides (AG) can be administered together with a β-lactam in patients with septic shock. Some authors propose administering a single dose of an AG combined with a β-lactam antibiotic in septic patients to extend the spectrum of antibiotic therapy. The aim of this study has been to investigate whether a single shot of AG when septic patients present at the Emergency Department (ED) is associated with acute kidney injury (AKI).

Methods: We retrospectively enrolled patients based on a 3-year internal registry of septic patients visited in the Emergency Department (ED) of Pordenone Hospital. We compared the patients treated with a single dose of gentamicin (in addition to the β-lactam) and those who had not been treated to verify AKI incidence.

Results: 355 patients were enrolled. The median age was 71 years (IQR 60-78). Less than 1% of the patients had a chronic renal disease. The most frequent infection source was the urinary tract (31%), followed by intra-abdominal and lower respiratory tract infections (15% for both). 131 patients received gentamicin. Unmatched data showed a significant difference between the two groups in AKI (79/131, 60.3% versus 102/224, 45.5%; p=0.010) and in infectious disease specialist's consultation (77/131, 59% versus 93/224, 41.5%; p=0.002). However, after propensity score matching, no significant difference was found.

Conclusion: Our experience shows that a single-shot administration of gentamicin upon admission to the ED does not determine an increased incidence of AKI in septic patients.

KEYWORDS: aminoglycosides, acute kidney injury, gentamicin, safety, sepsis

Introduction

Historically, sepsis has a high mortality, up to 50-75% [1]. The development of new antibiotic molecules has led to a significant reduction, but it still ranges from 30-50% even if treated according to recent guidelines [2]. Furthermore, pathogenic microorganisms have continued to develop resistance under selective antibiotic pressure, making the therapies increasingly complex, particularly in empirical approaches.

The choice of appropriate antibiotic treatment can reduce mortality [3]. For this reason, the real benefit of empirical combination therapy was assessed, particularly in critically ill patients. According to the Surviving Sepsis campaign [4], aminoglycosides (AG) can be administered together with a β-lactam in patients with septic shock (defined by the Sepsis-3 criteria). The spectrum of antibiotics is broadened in particular towards *Enterobacteriaceae* ESBL and *Pseudomonas aeruginosa*; the bacteria are attacked in two different ways, thus accelerating the elimination of pathogens [4, 5] in a possible synergistic effect. For patients presenting symptoms compatible with sepsis, some authors propose a single dose or short course (48-72 hours) of an AG in combination with a β-lactam antibiotic (that instead is taken for several days) on admission to the Emergency Department (ED), immediately after blood cultures are taken [6]. The AG dosage is based on body weight (5 to 7 mg/kg for gentamicin), and it is administered together with the first dose of β-lactam, regardless of renal function.

A study by David et al. showed that the risk of AKI following a single dose or a short course of AG in the empirical treatment of bacteremia increases compared to a regimen without AG [7]. The aim of this study has been to investigate whether a single shot of AG in the ED is associated with AKI in sepsis patients.

Materials and methods

Population and data collection

Septic patients were retrospectively enrolled at the ED of the Hospital of Pordenone by consecutive sampling, from 1st January 2017 to 31st December 2019, based on an internal registry of all patients admitted to the ED. Each patient gave informed consent for data acquisition, and the European Privacy Regulation 2016/679 for General Data Protection Regulation (GDPR) was respected. Patients were eligible if they met the third international consensus definition of sepsis. Exclusion criteria were age below 18, pregnancy, major trauma, cardiac arrest.

The primary aim was to determine whether a single initial dose of aminoglycoside (gentamicin) could lead to acute renal injury in a group of septic patients. Furthermore, we investigated which variables were correlated to the development of AKI.

We looked at demographic characteristics (age and sex), source of infection, immunodepression condition, the presence of a chronic kidney disease (defined as a decreased glomerular filtration rate of less than 60 mL/min/1.73 m2 for at least 3 months, according to the definition by KIDGO CKD Work Group [8]) or acute kidney injury (defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or an increase in serum creatinine to ≥1.5 times the baseline or a urine volume <0.5 mL/Kg/hour for six hours, according to the KDIGO definition), collection of at least one blood culture sample, length of stay in the hospital, the outcome of hospitalization (recovery, death, admission in ICU or a non-intensive care ward). It was also recorded whether a single dose of gentamicin was administered at the time of hospital admission, at the usual doses reported in the literature (5-7 mg/kg/dose IV).

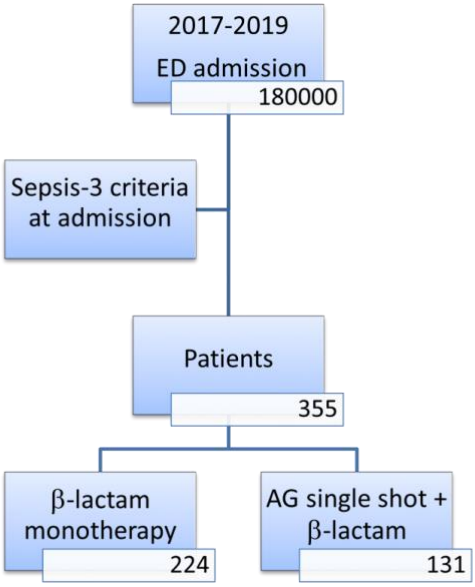

Figure 1: Flowchart of the cohort-registry enrollment. Septic patients were retrospectively enrolled at the ED of the Hospital of Pordenone by consecutive sampling, from 1st January 2017 to 31st December 2019, based on an internal registry of all patients admitted to the ED

Statistical analysis

Discrete variables were expressed as absolute value and percentage (%), while continuous variables were expressed as the median and interquartile range (IQR) for a non-parametric distribution. In the comparison between the groups, the distribution of the variables was verified using the Shapiro-Wilks test. The groups' differences were calculated through the Kruskal-Wallis test for continuous variables if not normally distributed (or Student's T-test if normally distributed); chi-square or exact Fisher's test was used for discrete variables. A p-value ≤of 0.05 was considered statistically significant. Corrections for pairwise comparisons were applied using the Benjamini and Hochberg method. A propensity score match based on the "nearest neighbor match" method was applied to compare the two study groups for baseline characteristics. A general linear multivariate regression was performed to verify the correlation between predictive variables and AKI using propensity score weighting. The statistical analysis was performed using the R environment (version 4.0.3, R Foundation for Statistical Computing. Vienna, Austria) with the following packages: "mice", "MatchIt", "compareGroups".

Results

During the 3 years, 355 patients were enrolled (Figure 1). The median age was 71 years (IQR 60-78), 56% was male, 1% had chronic kidney disease, 5% was considered immunosuppressed (a transplant patient, a patient on immunosuppressive therapy, a neoplastic patient in non-palliative treatment, a patient with rheumatological disorders). In 48% of cases, an infectious diseases consultant was involved. The most frequent infection source was the urinary tract (31%), followed by intra-abdominal and lower respiratory tract infections (15% for both). In 17% of cases, the source of the infection was not determined. The median length of stay was 4 days; 69% was in a low-intensity care ward. In-hospital mortality was around 5%. 131 patients were treated with a single dose of gentamicin. Acute renal injury occurred in 51% of cases (Table 1). Unmatched data showed a significant difference between the treated and non-treated groups as far as AKI (79/131, 60.3% versus 102/224, 45.5%; p=0.010) and the consultation of infectious disease specialists (77/131, 59% versus 93/224, 41.5%; p=0.002) were concerned. However, after propensity score matching, no

significant difference was found. No variables were significantly correlated with AKI in a general linear regression model.

		ALL	Unmatched			Matched		
			Control Group	Gentamicine Group	P-value	Control Group	Gentamicine Group	P-value
		N = 355	N = 224	N = 131		N = 131	N = 131	
Age (Years)		71 (60-78)	71 (61-78)	70 (59-78)	.536	71 (61-77)	70 (59-78)	.671
Sex (male)		199 (56.1%)	129 (57.6%)	70 (53.4%)	.516	71 (54.2%)	70 (53.4%)	1
Blood cultures taken		334 (94.1%)	207 (92.4%)	127 (96.9%)	.130	127 (96.9%)	127 (96.9%)	1
Source of infection					.			.
	Abdominal	52 (14.6%)	37 (16.5%)	15 (11.5%)		23 (17.6%)	15 (11.5%)	
	Bone	12 (3.4%)	6 (2.7%)	6 (4.6%)		5 (3.8%)	6 (4.6%)	
	Device	7 (2.0%)	4 (1.8%)	3 (2.3%)		3 (2.3%)	3 (2.3%)	
	Endocarditis	11 (3.1%)	8 (3.6%)	3 (2.3%)		5 (3.8%)	3 (2.3%)	
	Lung	53 (14.9%)	51 (22.8%)	2 (1.5%)		23 (17.6%)	2 (1.5%)	
	Neurological	7 (2.0%)	6 (2.7%)	1 (0.8%)		4 (3.1%)	1 (0.8%)	
	Skin	43 (12.1%)	32 (14.3%)	11 (8.4%)		19 (14.5%)	11 (8.4%)	
	UTI	109 (30.7%)	49 (31.9%)	60 (45.8%)		27 (20.6%)	60 (45.8%)	
	n.d.	61 (17.2%)	31 (13.8%)	30 (22.9%)		22 (16.8%)	30 (22.9%)	
Immunocompromised		18 (5.1%)	10 (4.5%)	8 (6.1%)	.667	6 (4.6%)	8 (6.1%)	.784
ID consultation		170 (47.9%)	93 (41.5%)	77 (58.8%)	*.002*	74 (56.5%)	77 (58.8%)	.803
CKD		3 (0.9%)	3 (1.3%)	0	.299	.	.	.
AKI		181 (51.0%)	102 (45.5%)	79 (60.3%)	*.010*	78 (59.5%)	79 (60.3%)	1
LOS (days)		4 (3-6)	5 (3-7)	4 (2-6)	.100	4 (3-6)	4 (2-6)	.384
Outcome					.597			.816
	Discharge	59 (16.6%)	37 (16.5%)	22 (16.8%)		25 (19.1%)	22 (16.8%)	
	Ward	245 (69.0%)	159 (71.0%)	86 (65.6%)		88 (67.2%)	86 (65.6%)	
	ICU	31 (9.0%)	18 (8.0%)	14 (10.7%)		10 (7.6%)	14 (10.7%)	
	Decease	19 (5.4%)	10 (4.5%)	9 (6.9%)		8 (6.1%)	9 (6.9%)	

Table I: Characteristics of the general population and crude and matched comparison by propensity score matching between groups of patients treated with aminoglycoside and not treated. ID = infectious diseases; CKD = chronic kidney disease; AKI = acute kidney injury; LOS = length of stay; ICU = intensive care unit

Discussion

Antibiotic therapy is the cornerstone of the treatment of critically ill patients with sepsis in ED. Combination therapy is widely used in the empirical approach to broaden the spectrum, particularly in the first few days, to increase the probability of appropriate initial treatment [9]. Although this is debated, AG in this setting seems to help broaden the gram-negative and gram-positive spectrum of coverage of empirical antimicrobial therapy. Furthermore, this therapy should provide rapid clearance of pathogens, especially from blood and urine.

Combined antibiotic therapy should be based on local resistance epidemiology and individual risk factors for resistance, including recent antibiotic use, length of hospitalization, and previously known colonization. In our Hospital, ESBL-producing Enterobacteriaceae are 11% of total isolates, much lower than the Italian and European average [10, 11].

In our study, presenting a 3-year series of consecutive septic patients enrolled in the context of an ED, we found an increase in AKI cases in subjects treated with AG in the raw comparison between the two groups. However, this difference was not replicated after applying a propensity score match analysis. This result leads to a multifactorial explanation of the development of AKI in septic patients, not related to AG exposure.

This result confirms what has been reported in the literature [12–15]. A short course or a single dose of AG does not seem to be associated with AKI, even in high-risk septic patients. Although older studies have obtained different results, they were likely influenced by a different pharmacokinetic pattern (longer cycles of multiple doses of AG per day) or by different bacterial strains, including nosocomial infections, being responsible for the sepsis. In 2015, Cobussen et al. found results similar to ours in patients developing AKI with or without AG administration, but an excess in mortality in the AG group was registered [12]. The mortality excess could be related to the worse presentation of patients treated with AG, and this can be deducted directly from the comparison between the SOFA scores, which is higher in the AG group. Moreover, patients in this group were more frequently in septic shock. The increased request for advice from the infectious disease specialist in our study indirectly reveals that patients in the AG group were more severe than the control group. Cobussen et al. obtained the same results in a large retrospective multicenter study [13], finding a similar pattern in both previously nephropathic and not nephropathic patients who had taken AG or just β-lactam. Regardless of the presence of AKI at hospital admission, AG did not worsen the renal function, and there was no delay in recovering a normal renal function (two weeks). In this study, patients in the AG group were more severely ill than the group that did not receive AG, as illustrated by the higher incidence of AKI at admission, qSOFA score, shock, ICU admissions, and 30-day mortality. Despite the difference in disease severity at admission, no significant differences were seen in AKI incidence during the first week of admission between groups.

Liljedahl Prytz et al. came to the same conclusions as us, hypothesizing that a single dose of AG is safer in avoiding chemical stress on an already saturated renal tubule [14]. Previous work by Carlsen et al. [15] showed no significant increase in AKI even using, as we did, a very sensitive staging method (KDIGO) to assess mild renal insufficiency and found an annual trend of AKI in a comparable percentage (80%) in both the AG and the monotherapy groups [15].

Our series notes that patients in the AG group more frequently presented abdominal or urinary infections rather than pulmonary infections. In these patients, septic syndrome likely evolved from complicated gram-negative bacterial infections. In 23% of cases, the infectious source was not detected.

Consultation with an infectious disease specialist most often suggests combination therapy with AG. This consultation has been associated with improved quality of care and better outcomes for several

infectious diseases, including S. aureus bacteremia and invasive candidiasis [16]. Many studies argue that specialist consultation is associated with lower mortality in patients with bloodstream infections due to the standardization of the sepsis approach with effective timing and tailored therapy [17–19]. Otherwise, the creation of a "ready-to-use" therapeutic protocol that takes into account the suspected site of infection, the patient's previous colonization, and risk factors for exposure (such as hemodialysis for *S. aureus*) could be a reasonable alternative in a context of resource optimization and good therapeutic management even in "hub-and-spoke" hospital organization [20].

Our study demonstrates the safety of a class of drugs that is too often seen as a "kidney killer" and therefore avoided or underdosed in patients considered at risk (severe septic patients for whom intense antibiotic therapy could be a lifesaver in the early hours). At the same time, there is no reason to administer a low dose when given as a loading dose. Cobussen et al. found that 20% of septic patients in a Dutch ED received an aminoglycoside underdose (equivalent to <5 mg/kg) [21]. These patients required intensive care admission more frequently. Interestingly, patients who received the smaller AG dose also had higher creatinine levels. Therefore, the single-dose AG not only does not cause an excess of AKI cases compared to controls but could also have a nephroprotective effect by counteracting the haemodynamic and direct mechanisms induced by the bacterial spread in the organism.

On the other hand, the high potential benefit of the β-lactam/AG combination is relevant in carbapenem sparing strategies when considering the increasing carbapenem resistance of gram-negative species even outside the hospital.

Our study, being retrospective, is subject to some limitations. For example, data on the microorganisms that supported infections were not reported, in particular, whether sensitive or resistant to AGs. Moreover, the β-lactam therapy was not standardized in both groups (mono and combination). Furthermore, we could not stratify the patients' initial conditions, for example, using the Charlson Score Index, due to the lack of the necessary variables. In any case, for the primary outcome we evaluated, the use of a propensity score match allowed us to eliminate the most relevant confounding factors associated with the development of AKI in septic patients in the ED.

Conclusion

According to the data we obtained, a single administration of gentamicin at the arrival time in the ED does not lead to an increased risk of AKI in septic patients.

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Declarations

1. *Funding:* No funds were provided to conduct this study.
2. *Conflicts of interest/Competing interests:* No conflict of interest for any author.
3. *Availability of data and material:* Data available by reasoned request.
4. *Code availability:* Not applicable.

5. *Ethics approval:* Retrospective cohort register exempted from ethics committee approval.
6. *Consent to participate:* Each patient gave informed consent for data acquisition, and the European Privacy Regulation 2016/679 for General Data Protection Regulation (GDPR) was respected.
7. *Consent for publication:* Each patient gave informed consent for data acquisition, and the European Privacy Regulation 2016/679 for General Data Protection Regulation (GDPR) was respected.
8. *Authors' contributions:* SV designed the study, collected the data, drafted the first draft and supervised the final draft; FC drafted the first draft and supervised the final draft; DO drafted the first draft and supervised the final draft, performed the statistical analysis; MC designed the study, collected the data; SF collected the data; AC collected the data; EP collected the data; LDS collected the data; DA collected the data; ML, LV and TB supervised the final draft.

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