

Risk of Acute Kidney Injury with Amikacin versus Gentamycin both in Combination with Metronidazole for Surgical Prophylaxis

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ABSTRACT

Introduction: Surgical site infection is one of the most important complication of surgery. It increases the mortality and morbidity. In order to decrease the incidence of surgical site infections perioperative antimicrobial prophylaxis has been recommended in certain types of clean and clean contaminated surgeries. Aminoglycosides are indicated as surgical prophylaxis for prevention of surgical site infection in patients with B-lactam allergy.

Aim: The present study was carried out to study and compare the renal safety profile of single high dose gentamycin and amikacin as surgical prophylactic antibiotic.

Materials and Methods: Prospective and randomized study was carried out on 100 patients for over one year period in a tertiary

care teaching hospital of western Uttar Pradesh, India. Patients in amikacin group received amikacin 15 mg/kg + metronidazole 500 mg intravenously single dose and those in the gentamycin group had gentamycin 5 mg/kg + metronidazole 500 mg intravenously single dose, one hour prior to incision.

Result: A total of 16% patients of amikacin group and 24% patients of gentamycin group developed acute kidney injury within one week of drug administration. The rise in serum creatinine was temporary as all patients had normal serum creatinine level at one month follow up.

Conclusion: Aminoglycoside intravenous single high dose is not safe as surgical prophylaxis.

Keywords: Aminoglycosides, Antibiotic prophylaxis, Surgical site infection, Prevention

INTRODUCTION

Surgical site infections (SSIs) are the most common healthcare-associated infection (HAI), accounting for 31% of all health-care associated infection among hospitalized patients [1]. The SSIs are classified as Superficial Incisional SSI, Deep Incisional SSI and Organ/space SSI. Superficial SSI involves only skin and subcutaneous tissue and occurs within 30 days of operative procedures. There are two specific types of superficial surgical SSI: Primary and Secondary. Deep Incisional SSI involves deep soft tissues (e.g. fascial and muscle layer) and occurs within 30 or 90 days of operative procedures. They are also of two types: Primary and Secondary. Organ/Space SSI occur within 30 or 90 days of operative procedures and involves any part of body deeper than fascial / muscle layer [2,3].

Most SSIs result from bacterial inoculation at the time of surgery. SSIs lead to adverse patient outcomes [4].

Antibiotics are administered prior to some surgical procedures to prevent surgical site infections. Antibiotic chosen should be active against microorganisms most commonly associated with wound infections following the surgical operations and against microorganisms endogenous to operating site [5].

Prophylactic antibiotic for gastrointestinal operations, biliary operations, genitourinary operations and gynaecological operations must cover enteric gram-negative bacilli, gram positive cocci, enterococci, clostridia and anaerobes. Recommended antibiotics for surgical prophylaxis in these conditions are B-lactams (cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam). Alternative drugs in patients with B-lactam allergy are clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone; metronidazole + aminoglycoside or fluoroquinolone. Single prophylactic intravenous doses of gentamycin 5 mg/kg body

weight, amikacin 15 mg/kg body weight and metronidazole 500 mg within one hour prior to incision have been recommended in adults [6].

The present study was planned to evaluate risk of acute kidney injury with gentamycin and amikacin, when used in certain surgical procedures as prophylactic antibiotics. The frequency of risk of acute kidney injury will determine the suitability of aminoglycoside as an alternative routinely recommended drug for surgical prophylaxis in B-lactam allergy.

MATERIALS AND METHODS

The present prospective and randomised study included 100 adult patients who underwent surgical procedures in which gentamycin or amikacin was used as a part of prophylactic antibiotic regimen. The study was carried out in co-ordination with the Department of General Surgery and Department of Pharmacology, Teerthanker Mahaveer Medical College and Research Centre (TMMC & RC), Moradabad during the period from January 2014 to February 2015. Written informed consents were obtained before enrolment in the study group.

Patients included in the present study were randomized into two groups i.e. amikacin group and gentamycin group with equal number of patients. All patients received single dose of prophylactic antibiotic within 60 minutes before incision.

Amikacin group patients received metronidazole 500 mg intravenous infusion and amikacin 15 mg/kg slow intravenous injection in 3 to 5 minutes. Gentamycin group patients received metronidazole 500 mg intravenous infusion and gentamycin 5 mg/kg slow intravenous injection in 3 to 5 minutes. Patients purchased drugs of branded companies from the market.

Inclusion Criteria

- Adult patients (aged > 18 years).
- Gastroduodenal surgeries: Resection for gastric or duodenal ulcers, resection for gastric carcinoma, repair of stricture of gastric outlet, perforated ulcer procedures, gastric bypass, gastric banding, gastroplasty.
- Small intestinal surgeries: Enterectomy with or without intestinal anastomoses or enterostomy, intestinal bypass, stricturoplasty.
- Biliary tract surgeries: cholecystectomy, exploration of common bile duct, Choledochenterostomy.
- Appendectomy: uncomplicated appendicitis.
- Urologic surgeries: Open or Laparoscopic renal surgery, urinary obstruction, urinary stone.
- Gynaecological surgeries: Vaginal, Abdominal or Laparoscopic Hysterectomy.
- Normal renal status.

Exclusion Criteria

- Paediatric patient.
- Overweight patient (BMI > 25 kg/m²).
- Patient with impaired renal status.
- Immunocompromised patient.
- Patient with co-morbid valvular heart disease.
- Patients requiring surgeries other than gastroduodenal, intestinal, biliary, urologic, colorectal, gynaecological conditions.
- Pregnant and lactating women.
- Patients hypersensitive to gentamycin and amikacin.
- Nephrotoxic patient.

Cardiac and vascular surgeries were not included in the study group because these surgeries are not performed at TMMC & RC. Ophthalmic and orthopaedic surgeries were also not included in the study because they are performed in their respective departments.

Before surgery, baseline serum creatinine level was estimated. After surgery, serum creatinine was measured daily for first seven postoperative days and maximal serum creatinine level during this period was recorded as after surgery value. Follow up was done at one month. Acute Kidney Injury (AKI) was defined as sudden decrease (in 48 hours) of renal function [Table/Fig-1].

Stage	Serum Creatinine
1	↑ SCr ≥ 26.5 μmol/L (≥ 0.3 mg/dL) or ↑ SCr ≥ 150-200 % (1.5-2.0 fold from baseline)
2	↑ SCr > 200-300 % (> 2-3 fold from baseline)
3	↑ SCr > 300 % (> 3 fold from baseline) or If baseline SCr ≥ 353.6 μmol/L (≥ 4 mg/dL) with an acute ↑ SCr ≥ 44.2 μmol/L (≥ 0.5 mg/dL)

[Table/Fig-1]: AKIN (Acute Kidney Injury) Network Staging of AKI [7].
SCr = Serum Creatinine, μmol/L = micromoles/litre, % = percentage, mg/dL = milligrams per decilitre, Normal SCr level = 60-120 μmol/L.

STATISTICAL ANALYSIS

Pearson Chi-square test, Independent student t-test and Paired-samples t-test were used for statistical analysis of various parameters as required. Data analysis was done with SPSS 21 and MS-excel 2008. The p-value of less than 0.05 was considered significant.

Ethical Clearance – The study was approved by Institutional Ethics Committee.

RESULTS

Eleven (22%) patients in amikacin group belonged to the age group of 61-70 years. In gentamycin group 13 (26%) patients belonged to the age group of 61-70 years [Table/Fig-2].

Age (years)	Amikacin group		Gentamycin group	
	n	%	n	%
<20	4	8.0	4	8.0
21-30	7	14.0	8	16.0
31-40	6	12.0	8	16.0
41-50	8	16.0	5	10.0
51-60	7	14.0	6	12.0
61-70	11	22.0	13	26.0
71-80	7	14.0	6	12.0
Total	50	100.0	50	100.0

[Table/Fig-2]: Age distribution of study group patients (n=100).
n = number of patients, % = percentage.

There were 26 (52%) females and 24 (48%) males in amikacin group. In gentamycin group, the male and female population were observed to be equal 25 (50%) [Table/Fig-3].

Gender	Amikacin group		Gentamycin group		p-value
	n	%	n	%	
Male	24	48.0	25	50.0	0.725
Female	26	52.0	25	50.0	
Total	50	100.0	50	100.0	

[Table/Fig-3]: Gender distribution of study group patients (n=100).
n = number of patients, % = percentage.

The mean serum creatinine value before intravenous prophylactic antibiotics in patients undergoing surgery was 0.87 mg/dL in both amikacin group and gentamycin group. In amikacin group mean serum creatinine was 0.81 mg/dL in females and 0.93 mg/dL in males. In gentamycin group the mean serum creatinine value was 0.82 mg/dL in females and 0.93 mg/dL in males. There was no significant difference in initial serum creatinine levels of the both groups [Table/Fig-4].

Variable	Amikacin group			Gentamycin group			p-value
	Male	Female	Total	Male	Female	Total	
	Mean	Mean	Mean±S.D	Mean	Mean	Mean±S.D	
Serum Creatinine	0.93	0.81	0.87±0.17	0.93	0.82	0.87±0.18	0.964

[Table/Fig-4]: Baseline serum creatinine level (mg/dL) before surgery
SD= Standard Deviation.

The mean serum creatinine value within one week after surgery observed was 1.19 mg/dL in amikacin group and 1.40 mg/dL in gentamycin group. Gender wise, in amikacin group the mean serum creatinine level was 1.10 mg/dL in females and 1.29 mg/dL in males. In gentamycin group the mean serum creatinine values was 1.24 mg/dL in females and 1.57 mg/dL in males. There was significant difference in final serum creatinine values of the both groups [Table/Fig-5].

Variable	Amikacin group			Gentamycin group			p-value
	Male	Female	Total	Male	Female	Total	
	Mean	Mean	Mean±S.D	Mean	Mean	Mean±S.D	
Serum Creatinine	1.29	1.10	1.19±0.30	1.57	1.24	1.40±0.52	0.046

[Table/Fig-5]: Serum creatinine level (mg/dL) within one week of surgery after prophylactic antibiotic.
SD= Standard Deviation.

The mean difference in final and initial serum creatinine values was observed to be 0.32 mg/dL in amikacin group and 0.53 mg/dL in gentamycin group. This difference was statistically significant [Table/Fig-6].

Acute kidney injury (AKI) stage 1 was observed in 8 (16%) patients of amikacin group and 10 (20%) patients of gentamycin group.

Stage 2 recorded in 2 (4%) in gentamycin group. Gender wise, 3 (6%) males and 5 (10%) females had AKI in amikacin group. In gentamycin group AKI was observed in 7 (14%) males and 5 (10%) females [Table/Fig-7].

Difference in variable of	Amikacin group	Gentamycin group	p-value
	Mean±S.D	Mean±S.D	
Serum Creatinine	0.32±0.22	0.53 ±0.38	0.007

[Table/Fig-6]: Difference in final and initial serum creatinine levels (mg/dL). SD= Standard Deviation.

Renal Status	Amikacin group			Gentamycin group		
	Male n (%)	Female n (%)	Total n (%)	Male n (%)	Female n (%)	Total n (%)
Normal	21(42)	21(42)	42(84)	18(36)	20(40)	38(76)
AKI	3(6)	5(10)	8(16)	7(14)	5(10)	12(24)
Total	24(48)	26(52)	50(100)	25(50)	25(50)	50(100)

[Table/Fig-7]: Incidence of AKI within one week of surgery after prophylactic antibiotic. n = number of patients, % = percentage, AKI = acute kidney injury

In amikacin group AKI was observed in 12% patients aged 61-70 years and no incidence occurred up in patients up to 50 years age. In gentamycin group 10% incidence of AKI was recorded in patients aged 61-70 years and 8% incidence was observed in patients up to 50 years age [Table/Fig-8].

Age (years)	Amikacin group		Gentamycin group	
	n	%	n	%
<20	0	0	1	2
21-30	0	0	1	2
31-40	0	0	2	4
41-50	0	0	0	0
51-60	1	2	2	4
61-70	6	12	5	10
71-80	1	2	1	2
Total	8	16	12	24

[Table/Fig-8]: Age distribution of AKI patients. n = number of patients, % = percentage.

All AKI patients had normal serum creatinine level at one month follow up. Study group included 5 patients requiring gastro-duodenal operations, 11 intestinal operations, 39 biliary operations, 28 urinary operations and 17 gynaecological operations.

DISCUSSION

In the present study, gentamycin as surgical prophylaxis has been observed to cause acute kidney injury (AKI) in 12 (24%) patients. Most AKI patients of gentamycin group had stage 1 and some had stage 2. Our results are comparable with Bell et al., Jensen et al., Criag et al., and Challangundla et al., [8-11].

Bell et al., studied risk of acute kidney injury (AKI) with gentamycin as surgical prophylaxis and observed that rates of AKI vary depending on clinical setting ranging from 6% to 25%. The majority of patients had transient stage 1 AKI but there were patients with persisting stages 2 and 3 [8].

Jensen et al., studied effect of single dose prophylactic gentamycin (5 mg/kg) and noticed a significant rise in the number of patients with a day one creatinine rise > 30 µmol/L [9]. Niesel et al., also noted AKI with rise in serum creatinine in 22% cases after receiving single prophylactic dose of gentamycin [12].

Craig et al., in their study concluded that single preoperative dose (240 mg) of gentamycin had no detrimental impact on renal function. There was, however, significant rise in serum creatinine [10]. Challangundla et al., reported AKI in 22% cases [11].

In our study all patients of AKI recovered in due course of time without any intervention where as in Challangundla et al., study three patients needed temporary haemodialysis [11].

Present study noted that older age was linked with acute kidney injury in both groups of patients but gentamycin has been observed to cause acute kidney injury in younger patients too. Our results are comparable to Bell et al., who also noted higher incidence of acute kidney injury in older patients with the use of aminoglycosides as surgical prophylaxis [8].

El-Mahallay et al., used aminoglycosides as prophylactic regimen in prevention of clear contaminated wound infections in cancer surgery and reported them to be safe and effective for prevention of SSI in clean contaminated operative procedures. Our results are not compatible with their results. This variation may be due to dose of aminoglycosides used. They used low dose of gentamycin (80 mg intravenously) or amikacin (500 mg intravenously) [13]. Aminoglycosides should be avoided in already existing nephrotoxic diseases and if given amikacin can be preferred over gentamycin. Gentamycin is a direct tubular toxin. After glomerular filtration, some gentamycin remains in the lysosomes of the renal proximal tubular epithelium. Prolonged dosing or supra therapeutic level increases the accumulation of the drug. It leaks from the lysosomes, entering and damaging the mitochondria. This leads to tubular epithelial cell death and the acute tubular necrosis-like picture [14].

LIMITATIONS

The serum aminoglycoside levels were not measured and biopsy could not be performed in patients who developed acute kidney injury.

CONCLUSION

Both gentamycin and amikacin are not safe for surgical prophylaxis in single high dose because of incidence of postoperative acute kidney injury particularly in the age group of 61-80 years. Hence aminoglycosides should not be routinely recommended as antimicrobial of choice in surgical prophylaxis unless alternative options are limited. Studies in larger population are required to further assess the risk factors associated with acute kidney injury and derive measures for early detection and treatment.

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