

The pharmacological and clinical aspects of using gentamicin in cardiac surgery

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Abstract

Surgical site infection (SSI) is a serious postoperative complication after cardiac surgery. The objective of this research is to examine the efficacy of administering gentamicin in minimizing the incidence of SSI while closely monitoring the therapeutic level of the drug. Prospective research included 50 Iraqi patients divided into two groups, 25 in each: Group 1 received a combination of flucloxacillin and ceftriaxone, while Group 2 received a combination of flucloxacillin and gentamicin 2 mg/kg of ideal body weight given before surgery, then 80 mg*3 for 48 hours after surgery. A total of five patients had an infection at the surgical site, with four patients in Group 1 and one patient in Group 2. Additionally, two patients in each group exhibited increased renal indices. Among the patients in Group 2, the highest concentration of gentamicin in the blood was $\leq 2.5 \mu\text{g/ml}$ for eight patients, while for 17 patients, the gentamicin concentration in the blood ranged from 3 to 4.4 $\mu\text{g/ml}$.

Keywords

surgical site infection, cardiac surgery, prophylactic antibiotics, gentamicin, survival

Introduction

Surgical site infections (SSIs) are defined as infections that arise during the first 30 days after a surgical procedure or within 1 year after introducing foreign material into the body (Remschmidt et al. 2023). The incidence of surgical site infection ranges from 0.5% to 3% among people who have surgery. Patients who develop a surgical site infection need a longer hospital stay of around 7 to 11 days compared to those who do not get an infection after surgery (Seidelman et al. 2023). Infections subsequent to cardiac surgery occur in 5% to 21% of cases, and severe infections can increase the risk of death after surgery by more than five times and prolong the recovery process

(de Tymowski et al. 2023a). Additionally, 47% of these patients need to stay in the hospital for more than 14 days, compared to only 5.9% of patients without a severe infection (Pérez-Granda et al. 2024). Consequently, infectious complications significantly raise the cost of healthcare. Nevertheless, these complications can be reduced through various straightforward measures, starting with modifying risk factors during the initial preoperative screening and continuing with careful monitoring of risk factors in the intensive care unit (ICU) shortly after surgery (Lepelletier et al. 2013).

The optimum period of antimicrobial prophylaxis after cardiothoracic surgeries is a subject of debate. However, it is generally recommended that prophylaxis be administered

during the surgery and for fewer than 24 hours thereafter (Droogh et al. 2023). Moreover, preventive antibiotics have been given for a maximum of 48 hours; however, there is not enough evidence to determine the most effective method (Zhang et al. 2023). Furthermore, researchers have observed that administering antimicrobial prophylaxis for a period of 1 to 4 days does not result in any decrease in SSIs when compared to single-dose prophylaxis or prophylaxis limited to the duration of the operation. Additionally, there is no advantage to prolonging the use of antimicrobial prophylaxis until the removal of indwelling lines, drains, and catheters (Ahmed et al. 2023). The outcomes of surgical site infections are influenced by the presence of antibiotic resistance. Gram-positive bacteria and gram-negative bacteria were isolated from the SSIs of 67% and 23% of the patients in the third-generation group and from 62% and 24% of the patients in the first-generation group, respectively. *Staphylococcus aureus* and coagulase-negative staphylococci, which are significant organisms causing SSIs in cardiac surgery, sometimes exhibit resistance to β -lactam medicines (Bae et al. 2022).

For the prevention of SSI, it is recommended to provide cephalosporins within 60 minutes after making the surgical incision. The primary objective of the rules about the appropriate timing of antibiotics is to ensure that sufficient levels of the medication are present in the bloodstream and tissues, above the minimum inhibitory concentration required to effectively combat the bacteria, hence reducing the risk of surgical site infections (Albacker et al. 2022). Vancomycin has been shown to be less efficient in preventing SSIs in cardiac surgery trials compared to anti-staphylococcal penicillins or first- or second-generation cephalosporins, particularly in cases where the infections are caused by methicillin-susceptible staphylococci (MSS) (de Tymowski et al. 2023b).

Remarkably, there has been little research that has directly examined the effectiveness of gentamicin and cephalosporins (Lebeaux et al. 2020). A meta-analysis conducted in 2015, which included 14 trials and a total of 22,135 patients, showed a significant decrease in the incidence of sternal wound infection when utilizing implanted local gentamicin-impregnated collagen sponges. However, in comprehensive and extensive research including 1502 patients who had heart surgery at 48 different medical facilities in the United States, the results mentioned before could not be validated (Elgariah and Omran).

Gentamicin is an aminoglycoside antibiotic that exhibits a wide range of antibacterial effects, mostly targeting Gram-negative bacteria, while its effectiveness against Gram-positive organisms is comparatively weaker. Gentamicin has significant efficacy against multidrug-resistant bacteria as well. Gentamicin is often used in conjunction with beta-lactam antibiotics to provide enhanced therapeutic efficacy via a synergistic effect, particularly in cases of gram-positive and multidrug-resistant bacterial infections (Zukowska and Zukowski 2022).

A straightforward diagnostic method for infection is the assessment of body temperature. Another easy and

cost-effective diagnostic approach is the assessment of the peripheral white blood cell (WBC) count and the differential cell count. There is a suggestion that the WBC and differential counts might be helpful in predicting bacterial infection. In addition, toxic granulations and vacuolization in the peripheral blood smear have been proposed as indicators of bacterial infection (Marik and Stephenson 2020).

This study aims to evaluate the efficacy of administering gentamicin in combination with flucloxacillin as a pre-medication and for 48 hours after surgery in reducing the incidence of surgical site infections in patients undergoing cardiac surgeries, as compared to using a combination of ceftriaxone and flucloxacillin. Additionally, the study aimed to observe the therapeutic level of gentamicin required to achieve an effective concentration of the drug.

Materials and methods

Study design

A prospective comparative study was conducted using an appropriate sample of 50 Iraqi patients who had undergone several types of cardiac surgeries. All patients underwent various types of cardiac surgery, such as coronary artery bypass graft (CABG), valve replacement, or device placement. The same surgical and anesthesia teams conducted the procedures.

Setting

A total of 50 patients (34 males and 16 females) were included in this study. These patients were admitted to the Surgical Department of the Iraqi Center for Heart Disease over a one-year period from January 2020 to January 2021.

Trial registration

The trial registration number is NCT06454643 and could be accessed at <https://clinicaltrials.gov/>.

Randomization

A computerized randomization method was used to allocate patients into two groups in a randomized manner. Following the first interview, the patients were sequentially assigned numbers and then randomized into two groups via the online program Research Randomizer, as seen in Fig. 1.

Sample size

The total number of participants was determined using G*Power software (RRID: SCR 013726), version 3.1.9.7. To achieve a 95% confidence interval, 90% power, a one-tailed alpha of 0.05, and an effect size of 0.46, the required sample size is 50 individuals.

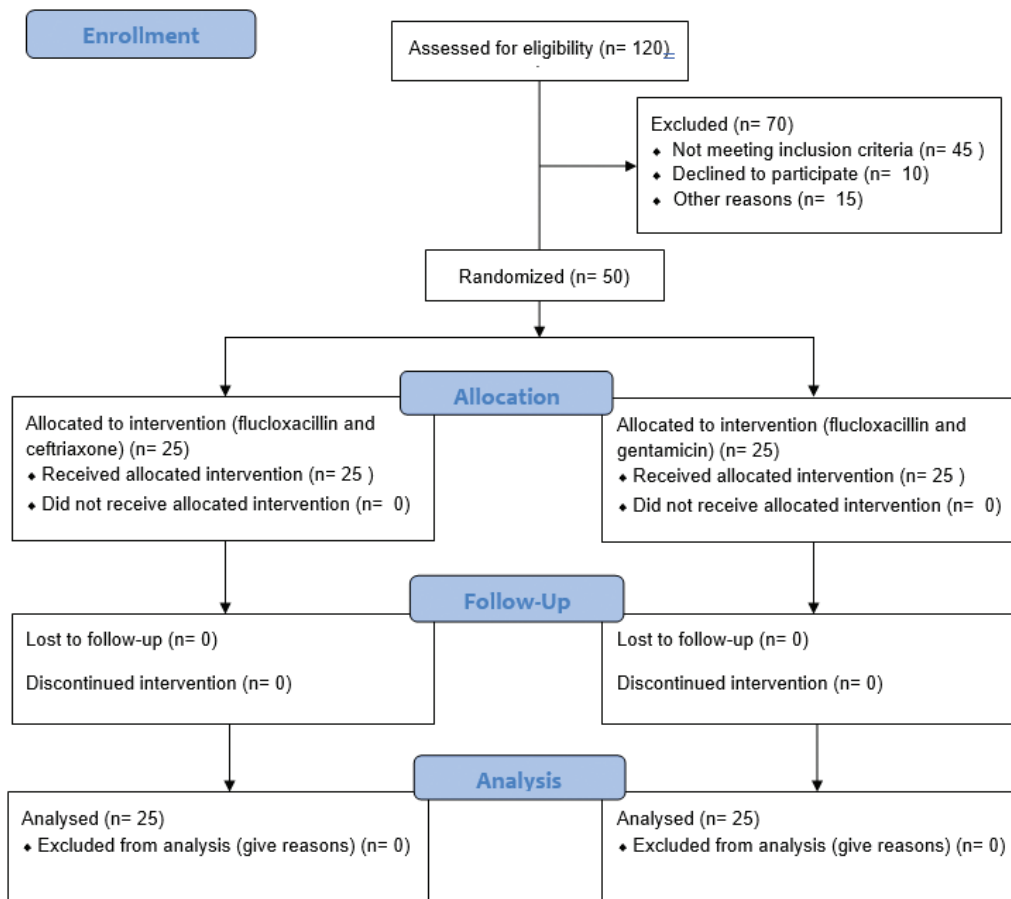


Figure 1. Participant flow diagram.

Inclusion criteria

The research included individuals of both sexes, aged 18 and above, who had undergone any type of cardiac surgery. The participant underwent different types of cardiac surgeries, including atrial septal defect (ASD) closure, aortic valve replacement (AVR), coronary artery bypass graft surgery (CABG), mitral valve replacement (MVR), cor-triatriatum closure, double valve replacement (DVR), right atrial myxoma (RAM), and ventricular septal defect (VSD) closure.

Exclusion criteria

Patients having a prior diagnosis of organ failure, patients already on antibiotics, patients with elevated baseline renal function tests before operation, or patients with contraindications to any of the prescribed medications were excluded from this study.

Study groups

Patients were divided into 2 groups as follows:

- Group 1 (n = 25): Patients received flucloxacillin and ceftriaxone 60 minute before incision and then continued for 48 hours as follows:

- Flucloxacillin 2 g (B BROWN, India) is given before surgery, then 1 g * 4 for 48 hours after the operation.
- Ceftriaxone 1 g (LDP. HN, Spain) is given before surgery, then 1 g * 2 for 48 hours after the operation.
- Group 2 (n = 25): Patients received flucloxacillin and gentamicin 60 minutes before incision and then continued for 48 hours, as follows:
 - Flucloxacillin 2 g is given before surgery, then 1 g * 4 for 48 hours after the operation.
 - Gentamicin 2 mg/kg (A. MENARINI, Italy) of ideal body weight given before surgery, then 80 mg * 3 for 48 hours after surgery.

The nursing staff in the ward gave the antibiotics according to the prescriptions in the patients' files.

Variables

Patients were followed for a duration of 5 days post-surgery. The diagnosis of postoperative infection relies on the clinical assessment conducted by a physician and the analysis of laboratory data, including WBCs, hemoglobin level (Hb), erythrocyte sedimentation rate (ESR), chest x-ray, and body temperature. Furthermore, left ventricular ejection fraction (LVEF), the average cardiopulmonary bypass (CPB) duration, and the average aortic cross-clamp (ACC) time were also documented for both groups.

The therapeutic drug monitoring (TDM) Unit conducted serum level monitoring of gentamicin using the Architect gentamicin kit (reference code 1P31-25) and the Architect i1000SR instrument (Abbott Laboratories). The assay employed a two-step immunoassay known as the Chemiflux method, which utilized CIMA technology for the quantitative determination of gentamicin in serum or plasma. In addition, the laboratory renal indices of all patients were monitored to assess the risk of gentamicin nephrotoxicity. This was done by measuring the maximum levels of serum creatinine and urea on the day of the operation, as well as on days 3 and 5 after the operation. The definition of acute kidney injury, as per the kidney disease: Improving Global Outcome (KDIGO) guideline, was considered to be an increase in serum creatinine to 1.5 times the baseline level or higher (Eckardt et al. 2023).

Sample preparation for gentamicin serum level

A blood sample is obtained using conventional venipuncture methods, which involve drawing 2 ml of blood into silicone-coated plastic tubes with gel barriers. The anti-coagulant that was used was EDTA. Ensure that the centrifuge process is sufficient to eliminate platelets. Follow the tube manufacturer's directions to centrifuge the sample, ensuring the plasma is separated from the blood cells correctly. Samples that have been divided are kept for a maximum of 7 days at a temperature range of 2 to 8 °C before undergoing testing. The test relies on the competition between the drug in the sample and the drug in a small particle to attach to the antibody sites of the gentamicin antibody reagent, which is coated on paramagnetic microparticles. This is achieved by combining the gentamicin-acridinium-labeled conjugate with the sample to create a reaction mixture. The microparticles coated with an anti-gentamicin substance adhere to both the gentamicin found in the sample and the acridinium-labeled conjugate. After washing, the pre-trigger and trigger solutions are introduced into the reaction mixture. The chemiluminescent reaction's outcome is quantified in terms of relative light units (RLUs). An inverse correlation exists between the quantity of gentamicin present in the sample and the RLUs identified by the optics of the Architect i System. The maximum concentration of gentamicin was detected within 30–60 minutes after administering the third dosage of the medicine.

Bias

The authors used rigorous measures to ensure that every eligible candidate had an equitable opportunity to be selected. Furthermore, the research was conducted to account for the specific settings, data accuracy, and quality assessment in order to minimize bias during the selection of the sample and the study methodology. This was achieved by utilizing a computer-based random number generator to generate an acceptable allocation sequence.

Statistical analysis

The data collection process employed Microsoft Office Excel 2019, while the acquired data were analyzed using SPSS 23 to compute the mean \pm SD, ranges, frequencies, and ratios. The P-value was calculated using the chi-square statistic, T-test, and two-table contingency table analysis methods. A significance threshold of 0.05 or below was used to ascertain the statistical significance of all the data provided in this study. The data was graphically presented using GraphPad Prism 8.2 on Microsoft Windows.

Results

The research included a total of 50 patients, with 25 patients in each group. Table 1 presents the demographic data and medical history of the patients under assessment.

Table 1. Demographic characteristics.

Demographic characteristics	Group 1 (n = 25)	Group 2 (n = 25)	P-value
Age	47.7 \pm 17.347	51.6 \pm 13.61	0.073
Gender	Male: 18 (72%) Female: 7 (28%)	Male: 16 (64%) Female: 9 (36%)	0.762
BMI	26.7 \pm 5.0	28.0 \pm 4.79	0.334
DM	8 (32%)	5 (20%)	0.333
CPB time (minutes)	100.52	109.22	0.154
ACC time (minutes)	77.08	70.72	0.323
LVEF \leq 40%	1	1	0.921

BMI: body mass index, DM: diabetes mellitus, CPB: cardiopulmonary bypass, ACC: average aortic cross-clamp, LVEF: left ventricular ejection fraction.

Group 1 consisted of 18 male patients (72%) and 7 female patients (28%), whereas Group 2 consisted of 16 male patients (64%) and 9 female patients (36%). In addition, the average age of patients in Group 1 was 47.76 \pm 17.34 years, whereas in Group 2, it was 51.60 \pm 13.61 years. In addition, 32% of patients in Group 1 were diagnosed with DM, whereas 25% of patients in Group 2 had this metabolic condition (P-value 0.333). Participants from both groups underwent different types of cardiac surgeries including atrial septal defect (ASD) closure, aortic valve replacement (AVR), coronary artery bypass graft surgery (CABG), mitral valve replacement (MVR), cor-triatriatum closure, double valve replacement (DVR), right atrial myxoma (RAM), ventricular septal defect (VSD) closure. Furthermore, it was observed that just one patient in each group had a left ventricular ejection fraction (LVEF) below 40% (P-value = 0.92). In Group 1, the average cardiopulmonary bypass (CPB) duration is 100.52 minutes, whereas in Group 2, it is 109.22 minutes (p-value = 0.154). Additionally, the average aortic cross-clamp (ACC) time is 77.08 minutes in Group 1 and 70.72 minutes in Group 2 (p-value 0.323).

There was no significant difference (P-value 0.349) in the incidence of infection between Group 1 and Group 2. In Group 1, 16% of patients (4 out of 25) had an

infection, while in Group 2, 4% of patients (1 out of 25) developed an infection. Additionally, both groups had the same number of patients with increased renal indices (2 patients in each group).

On the fifth day after the operation, there was no significant difference ($P > 0.05$) in the average white blood cell count between Group 1 (12.56 ± 4.87) and Group 2 (11.32 ± 2.4). Similarly, there was no significant difference ($P > 0.05$) in the average erythrocyte sedimentation rate between Group 1 (64.9 ± 29) and Group 2 (63.16 ± 18.9). Additionally, there was no significant difference ($P > 0.05$) in the average of hemoglobin level between Group 1 (10.89 ± 1.26 mg/dl) and Group 2 (11.12 ± 0.71 mg/dl), as indicated in Figs 2–4.

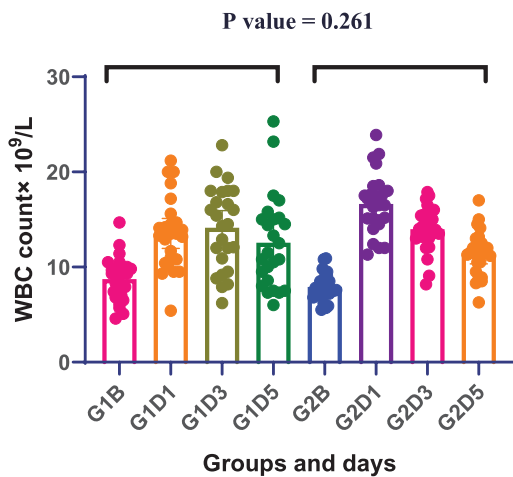


Figure 2. Changes in mean WBCs through baseline, day 1, day 3 and day 5 postoperatively in the studied patients' groups. (G1B = group 1 at baseline, G1D1 = group 1 at day 1, G1D3 = group 1 at day 3, G1D5 = group 1 at day 5, G2B = group 2 at baseline, G2D1 = group 2 at day 1, G2D3 = group 2 at day 3, G2D5 = group 2 at day 5). A T-test was employed in the statistical analysis.

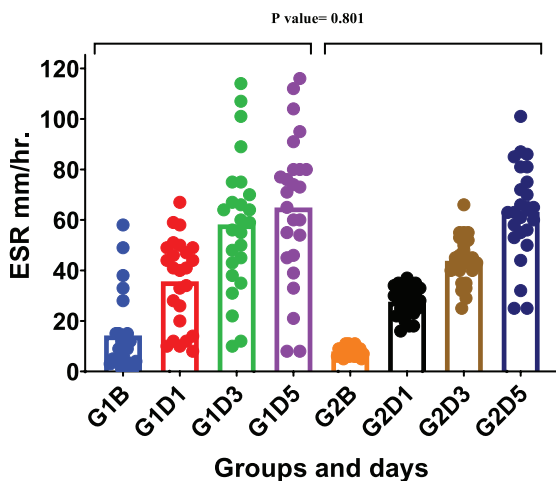


Figure 3. Changes in mean ESR through baseline, day 1, day 3 and day 5 postoperatively in the studied patients' groups. (G1B = group 1 at baseline, G1D1 = group 1 at day 1, G1D3 = group 1 at day 3, G1D5 = group 1 at day 5, G2B = group 2 at baseline, G2D1 = group 2 at day 1, G2D3 = group 2 at day 3, G2D5 = group 2 at day 5). T-test was employed in the statistical analysis.

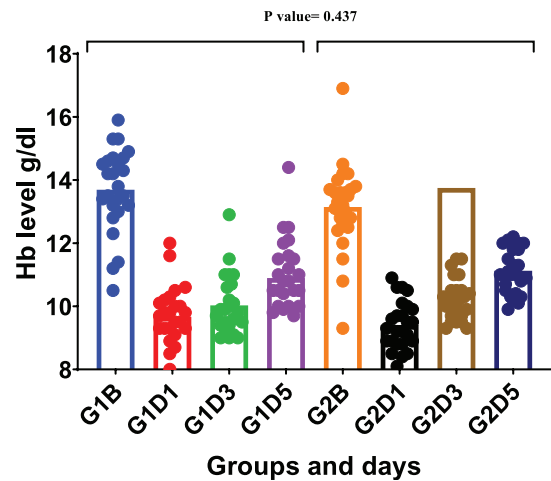


Figure 4. Changes in the mean Hb through baseline, day 1, day 3 and day 5 postoperatively in the studied patients' groups. (G1B = group 1 at baseline, G1D1 = group 1 at day 1, G1D3 = group 1 at day 3, G1D5 = group 1 at day 5, G2B = group 2 at baseline, G2D1 = group 2 at day 1, G2D3 = group 2 at day 3, G2D5 = group 2 at day 5). A T-test was employed in the statistical analysis.

Group 2 patients were assessed for the peak level of gentamicin concentration. In Table 2, it is seen that among the 25 patients, 7 (32%) had a concentration of less than 3 µg/ml, while 17 (68%) had a value between 3 and less than 4.5 µg/ml. None of the patients had a concentration equal to or more than 4.5 µg/ml.

Table 2. The range of gentamicin peak concentration in the studied group of patients.

Gentamicin concentration	No. of patient	Percentage
≤ 2.9 mcg/ml	8	32%
3–4.5 mcg/ml	17	68%
≥ 4.5 mcg/ml	0	0

Discussion

The combination of systemic hypothermia, coagulopathy accompanied by bleeding and the need for transfusions can make patients performing cardiac surgery more susceptible to infection (Banasiwicz et al. 2023). This can result in the need for additional extensive surgery, longer hospital stays, increased costs, higher mortality rates, and reduced long-term survival (Erdoes et al. 2023). Prophylactic therapy for cardiac surgery has been indicated by recent recommendations from the Scottish Intercollegiate Network, the National Institute for Health and Clinical Excellence, and the American College of Cardiology/American Heart Association Task Force (Ackah et al. 2021; Boriani et al. 2021; Dehmer et al. 2020; Wang and Fosbøl 2022). These guidelines do not provide clear suggestions about specified antibacterials. In the surgical ward of the Iraqi Center for Heart Disease, the standard practice is to administer amoxicillin, flucloxacillin, and ceftriaxone as preventive antibiotics before surgery. After the operation, the patient is then given vancomycin and ceftriaxone until they are discharged. The

present investigation used flucloxacillin and gentamicin antibiotics before the operation and maintained their use for 48 hours after the operation (Group 2). A comparison was made between the efficacy of this treatment regimen and the regimen of flucloxacillin and ceftriaxone (Group 1). This study found that the incidence of SSI in Group 1 was 16%, while the incidence of SSI in Group 2 was 4%. However, there were no significant differences in the rate of SSI between the two groups. This study aligns with a prior analysis conducted by White et al., which aimed to assess the safety and effectiveness of short-course gentamicin-based prophylaxis. The study suggests that a dosage of 2 mg/kg of ideal body weight, combined with a glycopeptide or flucloxacillin, was equally effective compared to a cephalosporin regimen (White et al. 2013).

The incidence of increased renal indices was comparable in both groups 1 and 2. The findings indicated that the flucloxacillin-gentamicin regimen (Group 2) resulted in a reduced rate of surgical site infections without any increase in the occurrence of renal damage. The decreased likelihood of acute renal impairment in a gentamicin-based treatment regimen may be attributed to enhanced defense against perioperative infection, a well-documented factor in the development of acute kidney damage. While our research did not demonstrate statistical significance, it is conceivable that it has clinical significance. The Scottish government set a goal in 2009 to decrease the incidence of *Clostridium difficile* infection by 30% over a period of 2 years. As a result, Scottish hospitals switched from using cephalosporins to gentamicin for surgical antibiotic prophylaxis. They investigated the incidence of postoperative acute renal damage before and after implementing this policy modification. The research sample consisted of 12,482 adult individuals who underwent surgical procedures. The modification in antibiotic policy did not result in a substantial rise in acute renal damage among the studied groups (Bell et al. 2014).

The number of white blood cells increased in all patients in groups 1 and 2 starting from the first day after the operations. The count reached its highest level on the third day and then decreased on the fifth day. This increase and subsequent decrease are a characteristic feature of the initial systemic inflammatory and stress response that occurs following heart surgery (Bain et al. 2023). The rise in white blood cell count shown here aligns with the findings of research conducted by Sotir Lako et al. In their study, the average levels of leukocytes and neutrophils showed a quick increase, reaching their peak on the second day after surgery and thereafter returning to normal levels within a period of 21 days (Lako et al. 2015). In this research, there were no significant differences in the ESR level. However, the ESR level continued to increase from day 1 after the operations and reached its peak on day 5 in both Group 1 and Group 2. The mean ESR at day 5 postoperatively was (64.9 ± 29) in Group 1 and (63.16 ± 18.9) in Group 2. This phenomenon may be attributed to the systemic inflammatory response that occurs after heart surgery. This finding is in line with the research conducted by Eissa Bilehjani et al., which demonstrated an elevation in the erythrocyte sedimentation rate

after cardiac surgery (Bilehjani et al. 2017). The hemoglobin level experienced a significant decrease on the first day after surgery in both group 1 and group 2. Subsequently, there was a slight increase in Hb levels by day 5. This observed pattern could be attributed to blood loss during and after the surgery. These findings align with previous studies that have reported mild to moderate fluctuations in Hb levels following coronary artery bypass grafting (CABG) surgery. Typically, Hb levels return to normal and preoperative values within 1–3 months post-surgery (Senage et al. 2021; Khalaji et al. 2023; Rogova et al. 2023).

In the present study, peak gentamicin levels were measured for all patients in group 2. Among these patients, 38.5% had concentrations below 3 µg/ml, 61.5% had concentrations ranging from 3 µg/ml to less than 4.5 µg/ml, and none of the patients had concentrations equal to or more than 4.5 µg/ml. Another study has demonstrated that the highest level of gentamicin in the bloodstream is between 3 and 4 µg/ml. This concentration is sufficient when combined with penicillins to effectively treat infective endocarditis. These findings emphasize the importance of therapeutic drug monitoring to ensure that gentamicin reaches the necessary therapeutic concentration, particularly in cases of severe infection (Bauer 2008; Hodiamont et al. 2022).

Study strengths and limitations

This study is one of the largest studies on SSI in cardiac surgery and, more specifically, on the use of gentamicin. The inclusion of patients and their surgical management were stable over time. Thus, the SSI rate was stable throughout the study.

This research was conducted during the time of the COVID-19 pandemic, which posed challenges in patient care and data gathering. Additionally, the surgical unit was temporarily closed for many months. This research pertains to a regional database from a single institution. It is probable that the selection of patients, choice of treatment, and care during the perioperative phase are significant factors that influence SSI. Furthermore, these parameters may differ across various cardiac surgery units. The research has a limited sample size. The duration of the follow-up period was limited to a short duration.

Conclusion

A short course of flucloxacillin in combination with gentamicin as antibiotic prophylaxis was shown to be as effective as a cephalosporin regimen in avoiding infection after heart surgery. The regular administration of a small dose of gentamicin did not result in a higher occurrence of acute kidney impairment.

Conflict of interests

The authors have declared that no competing interests exist.

Funding

The authors have no funding to report.

Ethics approval

The scientific and ethical committees of Iraqi Board of Medical Specializations officially accepted the study protocol on 8/9/2019 with approval number 1420.

References

- Ackah JK, Neal L, Marshall NR, Panahi P, Lloyd C, Rogers LJ (2021) Antimicrobial prophylaxis in adult cardiac surgery in the United Kingdom and Republic of Ireland. *Journal of Infection Prevention*, 22: 83–90. <https://doi.org/10.1177/1757177420971850>
- Ahmed NJ, Haseeb A, Alqarni A, Algethamy M, Mahrous AJ, Alshehri AM, Alahmari AK, Abuhussain SSA, Bashawri AMA, Khan AH (2023) Antibiotics for preventing infection at the surgical site: Single dose vs. multiple doses. *Saudi Pharmaceutical Journal* 31: 101800. <https://doi.org/10.1016/j.jsps.2023.101800>
- Albacker TB, Alqattan H, Alqahtani SA, Alamro S, Alsuwaidan N, Alaloola A, Eldemerdash A, Bakir B (2022) Serum level of prophylactic antibiotics in cardiac surgery and its implication on surgical site infection (SSI). *American Journal of Cardiovascular Disease* 12: 233. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9490157/>
- Bae S-J, Kim I, Song J, Chung E-S (2022) The effect of first-and third-generation prophylactic antibiotics on hospitalization and medical expenditures for cardiac surgery. *Journal of Cardiothoracic Surgery* 17: 15. <https://doi.org/10.1186/s13019-022-01763-4>
- Bain CR, Myles PS, Corcoran T, Dieleman JM (2023) Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. *Anaesthesia* 78: 356–370. <https://doi.org/10.1111/anae.15896>
- Banasiewicz T, Machała W, Wysocki MB, Lesiak M, Krych S, Lange M, Hogendorf P, Durczyński A, Cwaliński J, Bartkowiak T (2023) Principles of minimize bleeding and the transfusion of blood and its components in operated patients-surgical aspects. *Polski Przegląd Chirurgiczny [Polish Journal of Surgery]* 95(5): 14–39. <https://doi.org/10.5604/01.3001.0053.8966>
- Bauer LA (2008) *Applied clinical pharmacokinetics*, McGraw-Hill Medical New York. <https://www.amazon.com/Applied-Clinical-Pharmacokinetics-Larry-Bauer/dp/0071794581>
- Bell S, Davey P, Nathwani D, Marwick C, Vadeloo T, Sneddon J, Patton A, Bennie M, Fleming S, Donnan PT (2014) Risk of AKI with gentamicin as surgical prophylaxis. *Journal of the American Society of Nephrology* 25: 2625–2632. <https://doi.org/10.1681/ASN.2014010035>
- Bilehjani E, Fakhari S, Farzin H, Yaghoubi A, Mirinazhad M, Shadvar K, Dehghani A, Aboalayi P (2017) The correlation between preoperative erythrocyte sedimentation rate and postoperative outcome in adult cardiac surgery. *International Journal of General Medicine* 10: 15–21. <https://doi.org/10.2147/IJGM.S121904>
- Boriani G, Kennergren C, Tarakji KG, Wright DJ, Ahmed FZ, McComb JM, Goette A, Blum T, Biffi M, Green M (2021) Cost-effectiveness analyses of an absorbable antibacterial envelope for use in patients at increased risk of cardiac implantable electronic device infection in Germany, Italy, and England. *Value in Health* 24: 930–938. <https://doi.org/10.1093/europace/euad159>
- De Tymowski C, Sahnoun T, Provenchere S, Para M, Derre N, Mutuon P, Duval X, Grall N, Iung B, Kernéis S (2023a) Impact of antibiotic prophylaxis on surgical site infections in cardiac surgery. *Antibiotics* 12: 85. <https://doi.org/10.3390/antibiotics12010085>
- De Tymowski C, Sahnoun T, Provenchere S, Para M, Derre N, Mutuon P, Duval X, Grall N, Iung B, Kernéis S, Lucet J-C, Montravers P (2023b) Impact of Antibiotic Prophylaxis on Surgical Site Infections in Cardiac Surgery. *Antibiotics [Online]* 12(1): 85. <https://doi.org/10.3390/antibiotics12010085>
- Dehmer GJ, Badhwar V, Bermudez EA, Cleveland Jr JC, Cohen MG, D'agostino RS, Ferguson Jr TB, Hendel RC, Isler ML, Jacobs JP (2020) 2020 AHA/ACC key data elements and definitions for coronary revascularization: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop clinical data standards for coronary revascularization). *Journal of the American College of Cardiology* 75: 1975–2088. <https://doi.org/10.1161/HCQ.0000000000000059>
- Droogh DHM, Groen JV, De Boer MGJ, Van Prehn J, Putter H, Bonsel BA, Van Eijck CHJ, Vahrmeijer AL, Van Santvoort HC, Groot Koerkamp B (2023) Prolonged antibiotic prophylaxis after pancreatoduodenectomy: systematic review and meta-analysis. *British Journal of Surgery* 110: 1458–1466. <https://doi.org/10.1093/bjs/znad213>
- Eckardt K-U, Delgado C, Heerspink HJL, Pecoits-Filho R, Ricardo AC, Stengel B, Tonelli M, Cheung M, Jadoul M, Winkelmayer WC (2023) Trends and perspectives for improving quality of chronic kidney disease care: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International* 104: 888–903. <https://doi.org/10.1016/j.kint.2023.05.013>
- Elgariah M, Omran T (2024) Effect of perioperative antibiotic prophylaxis on surgical site infections complicating conventional cardiothoracic surgery. *The Egyptian Journal of Hospital Medicine* (April 2024) 95: 1969–1974. <https://doi.org/10.21608/ejhm.2024.356009>
- Erdoes G, Faraoni D, Koster A, Steiner ME, Ghadimi K, Levy JH (2023) Perioperative considerations in management of the severely bleeding coagulopathic patient. *Anesthesiology* 138: 535–560. <https://doi.org/10.1097/ALN.0000000000004520>
- Hodiamont CJ, Van Den Broek AK, De Vroom SL, Prins JM, Mathôt RAA, Van Hest RM (2022) Clinical pharmacokinetics of gentamicin in various patient populations and consequences for optimal dosing for gram-negative infections: an updated review. *Clinical pharmacokinetics* 61: 1075–1094. <https://doi.org/10.1007/s40262-022-01143-0>

Consent to participate

Before recruiting each individual, the researcher explained the study's goal and got written consent.

Data availability

Further data is available from the authors upon reasonable request. Trial registration: NCT06454643 at <https://clinicaltrials.gov/>.

- Khalaji A, Ajam A, Sheikhy A, Behnoush AH, Fallahzadeh A, Bagheri J, Mansourian S, Momtahan S, Masoudkabar F, Hosseini K (2023) Mortality across the spectrum of hemoglobin level in patients undergoing surgical coronary revascularization. *Clinical Cardiology* 46: 535–542. <https://doi.org/10.1002/clc.24004>
- Lako S, Dedej T, Nurka T, Ostreni V, Demiraj A, Xhaxho R, Prifti E (2015) Hematological changes in patients undergoing coronary artery bypass surgery: a prospective study. *Medical Archives* 69: 181. <https://doi.org/10.5455/medarh.2015.69.181-186>
- Lebeaux D, Fernández-Hidalgo N, Pilmis B, Tattevin P, Mainardi JL (2020) Aminoglycosides for infective endocarditis: time to say goodbye? *Clinical Microbiology and Infection* 26: 723–728. <https://doi.org/10.1016/j.cmi.2019.10.017>
- Lepelletier D, Bourigault C, Roussel JC, Lasserre C, Leclère B, Corvec S, Patier S, Lepoivre T, Baron O, Despins P (2013) Epidemiology and prevention of surgical site infections after cardiac surgery. *Médecine et maladies infectieuses* 43: 403–409. <https://doi.org/10.1016/j.medmal.2013.07.003>
- Marik PE, Stephenson E (2020) The ability of Procalcitonin, lactate, white blood cell count and neutrophil-lymphocyte count ratio to predict blood stream infection. Analysis of a large database. *Journal of Critical Care* 60: 135–139. <https://doi.org/10.1016/j.jcrc.2020.07.026>
- Pérez-Granda MJ, Barrio JM, Cuerpo G, Valerio M, Muñoz P, Hortal J, Pinto AG, Bouza E (2024) Infectious complications following major heart surgery from the day of the surgery to hospital discharge. *BMC Infectious Diseases* 24: 73. <https://doi.org/10.1186/s12879-023-08972-9>
- Remschmidt B, Schwaiger M, Gaessler J, Wallner J, Zemann W (2023) Surgical site infections in orthognathic surgery: prolonged versus single-dose antibiotic prophylaxis. *International Journal of Oral and Maxillofacial Surgery* 52: 219–226. <https://doi.org/10.1016/j.ijom.2022.06.002>
- Rogova O, Herzog K, Al-Majdoub M, Miskelly M, Lindqvist A, Bennet L, Hedenbro JL, Wierup N, Spégel P (2023) Metabolic remission precedes possible weight regain after gastric bypass surgery. *Obesity* 31: 2530–2542. <https://doi.org/10.1002/oby.23864>
- Seidelman JL, Mantyh CR, Anderson DJ (2023) Surgical site infection prevention: a review. *JAMA* 329: 244–252. <https://doi.org/10.1001/jama.2022.24075>
- Senage T, Gerrard C, Moorjani N, Jenkins DP, Ali JM (2021) Early post-operative bleeding impacts long-term survival following first-time on-pump coronary artery bypass grafting. *Journal of Thoracic Disease* 13: 5670. <https://doi.org/10.21037/jtd-21-1241>
- Wang A, Fosbøl EL (2022) Current recommendations and uncertainties for surgical treatment of infective endocarditis: a comparison of American and European cardiovascular guidelines. *European Heart Journal* 43: 1617–1625. <https://doi.org/10.1093/eurheartj/ehab898>
- White RW, West R, Howard P, Sandoe J (2013) Antimicrobial Regime for Cardiac Surgery: The Safety and Effectiveness of Short-Course Flucloxacillin (or Teicoplanin) and Gentamicin-Based Prophylaxis. *Journal of Cardiac Surgery: Including Mechanical and Biological Support for the Heart and Lungs* 28: 512–516. <https://doi.org/10.1111/jocs.12155>
- Zhang H-T, Wang K, Li Z-S, Wang C-S, Han X-K, Chen W, Fan F-D, Pan J, Zhou Q, Cao H-L (2023) Diagnosis of early bacterial pneumonia and sepsis after cardiovascular surgery: A diagnostic prediction model based on LASSO logistic regression. *Journal of Inflammation Research* 16: 3983–3996. <https://doi.org/10.2147/JIR.S423683>
- Zukowska A, Zukowski M (2022) Surgical site infection in cardiac surgery. *Journal of Clinical Medicine* 11: 6991. <https://doi.org/10.3390/jcm11236991>

Appendix 1

Reporting checklist for randomized trial. Based on the CONSORT guidelines.

Table A1. Reporting checklist for randomized trial.

	Reporting Item	Page Number
Title and Abstract		
Title	#1a Identification as a randomized trial in the title.	1
Abstract	#1b Structured summary of trial design, methods, results, and conclusions	1
Introduction		
Background and objectives	#2a Scientific background and explanation of rationale	1,2
Background and objectives	#2b Specific objectives or hypothesis	1,2
Methods		
Trial design	#3a Description of trial design (such as parallel, factorial) including allocation ratio.	3
Trial design	#3b Important changes to methods after trial commencement (such as eligibility criteria), with reasons	3
Participants	#4a Eligibility criteria for participants	4
Participants	#4b Settings and locations where the data were collected	4
Interventions	#5 The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	#6a Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	5
Outcomes	#6b Any changes to trial outcomes after the trial commenced, with reasons	6
Sample size	#7a How sample size was determined.	6
Sample size	#7b When applicable, explanation of any interim analyses and stopping guidelines	6
Randomization - Sequence generation	#8a Method used to generate the random allocation sequence.	

	Reporting Item	Page Number
Randomization - Sequence generation	#8b Type of randomization; details of any restriction (such as blocking and block size)	
Randomization - Allocation concealment mechanism	#9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3
Randomization - Implementation	#10 Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	3
Blinding	#11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	3
Blinding	#11b If relevant, description of the similarity of interventions	3
Statistical methods	#12a Statistical methods used to compare groups for primary and secondary outcomes	6
Statistical methods	#12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results		6
Participant flow diagram (strongly recommended)	#13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	6
Participant flow	#13b For each group, losses and exclusions after randomization, together with reason	6
Recruitment	#14a Dates defining the periods of recruitment and follow-up	6
Recruitment	#14b Why the trial ended or was stopped	6
Baseline data	#15 A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	#16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6
Outcomes and estimation	#17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7
Outcomes and estimation	#17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	7–10
Ancillary analyses	#18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7–10
Harms	#19 All-important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	
Discussion		11
Limitations	#20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalizability	#21 Generalizability (external validity, applicability) of the trial findings	12
Interpretation	#22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12
Registration	#23 Registration number and name of trial registry	12
Other information		
Interpretation	#22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Registration	#23 Registration number and name of trial registry	
Protocol	#24 Where the full trial protocol can be accessed, if available	
Funding	#25 Sources of funding and other support (such as supply of drugs), role of funders	12