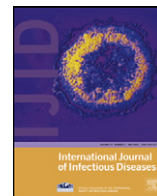




Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid



A double-blind study of the efficacy and safety of multiple daily doses of amikacin versus one daily dose for children with perforated appendicitis in Costa Rica[☆]

Víctor Pérez^{a,b,*}, Desirée Saéñz^b, Juan Madriz^a, Michael Harhay^c, Juvenal Feoli^a,
Maria Castro^a, Carla Odio^a

^a Intensive Care Unit, National Children's Hospital, San José, PO Box 1654-1000, Costa Rica

^b School of Medicine, University of Costa Rica, San José, Costa Rica

^c Public Health Consultant, Philadelphia, PA, USA

ARTICLE INFO

Article history:

Received 20 August 2010

Received in revised form 4 April 2011

Accepted 26 April 2011

Corresponding Editor: William Cameron,
Ottawa, Canada.

Keywords:

Amikacin

ODD (once daily dosing)

MDD (multiple daily dosing)

Appendicitis

Costa Rica

SUMMARY

Background: There is evidence that aminoglycosides given in a single daily dose (once daily dose, ODD) are as effective and safe as multiple daily doses (MDD). However, the published pharmacokinetic and pharmacodynamic data are overly representative of pediatric populations in Europe and the USA, and not representative of low or middle-income countries such as Costa Rica, in which the patient population might differ from those in higher income settings.

Methods: A double-blind, randomized clinical trial of the efficacy and safety of ODD vs. MDD amikacin therapy was conducted for children aged 2–12 years with an intraoperative diagnosis of perforated appendicitis. One hundred patients were randomized following a one-to-one randomization to receive either amikacin 7.5 mg/kg every 8 h (MDD) or 22.5 mg/kg as a single dose (ODD). Patients in both groups were given clindamycin 10 mg/kg every 6 h. Efficacy was evaluated by the occurrence of intra-abdominal abscesses, documented by abdominal ultrasound, and therapeutic failure. Safety was determined by the presence of renal or cochlear toxicity.

Results: Fifty patients were enrolled in each group. There were no statistically significant differences in the incidence of intra-abdominal abscesses or therapeutic failures, or in the occurrence of cochlear or renal toxicity, between the MDD and ODD treatment groups.

Conclusions: In this patient population of Costa Rican children with perforated appendicitis, we found that amikacin ODD is as safe and effective as the MDD regimen. This could have implications for national health systems such as that in Costa Rica, as ODD is presumably a more economic option and may reduce the cost of antibiotic treatment in patients with perforated appendicitis. This would need to be confirmed through an economic analysis, which is outside the purview of this paper.

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1. Introduction

Aminoglycosides are commonly used for the treatment of children with perforated appendicitis, despite their potential to cause ototoxicity and nephrotoxicity.^{1,2} However, there is still debate, even in clinical settings where resources are not limited, as to whether these antibiotics should be given in multiple daily doses (MDD) or as a single daily dose (once daily dose, ODD). ODD has been shown to achieve higher peak plasma concentrations with relatively undetectable trough concentrations, and thus to

exert a high concentration-dependent bactericidal activity, greater post-antibiotic effect, lower risk of adaptive resistance, and reduced accumulation in the inner ear and renal proximal tubules.^{3–5} Recent systematic reviews of the efficacy and safety of giving aminoglycosides as an ODD to children and neonates have concluded that ODD is preferable to MDD, because ODD both minimizes costs and simplifies administration while remaining efficacious and safe.^{6,7} However, most empirical data in these reviews are derived from well developed American and European clinical settings in pediatric populations.^{8,9} As a result the promulgated standard of care may not be the same for other populations with potential metabolic differences in drug handling. As the healthcare systems in low- and middle- income countries continue to develop, it is critical that clinical investigation follows that of the countries that generally dominate the peer reviewed literature so that appropriate and cost-effective patient care evolves.

[☆] Trial registration: Estudio 229-08-04-00017. Comparación de la eficacia y seguridad de la amikacina, administración única diaria contra tres dosis diarias en pacientes pediátricos con apendicitis aguda perforada.

* Corresponding author. Tel.: +506 22552239; fax: +506 22552239.

E-mail address: vperezh@hnn.sa.cr (V. Pérez).

For example, although there are well designed studies comparing the two amikacin dosing regimens in the pediatric population,^{10–13} we found only one other prospective study in the English language literature conducted in children with peritonitis.¹⁴ As most systematic reviews use English search terms and peer review literature only, the above-mentioned populations are not represented in existing analysis. Thus, to further build the available empirical pharmacodynamic, pharmacokinetic, and outcome data, we undertook a prospective, double-blind, controlled study to compare the effectiveness and safety of ODD vs. MDD of amikacin in patients with perforated appendicitis in a patient population in a middle-income country, Costa Rica, for which little empirical data exist.

2. Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information (see [Supplementary Information, appendices 1 and 2](#)).

2.1. Participants

This was a prospective, randomized, double-blind, single-center study. The patient population consisted of 100 children aged between 2 and 12 years, with a diagnosis of perforated appendicitis in the operating room at the Department of General Surgery, National Children's Hospital in San José, Costa Rica. Fifty patients were assigned to each group following a one-to-one randomization.

Exclusion criteria included: known allergy to aminoglycosides, known impaired renal function, known hearing loss or vestibular disease, neutropenia, cystic fibrosis, neuromuscular disease, concomitant administration of furosemide or other nephrotoxic drugs, and history of treatment with aminoglycosides in the preceding 2 weeks. Informed consent was obtained from parents or legal guardians of the patients prior to enrollment.

2.2. Ethics

Original approval for this study protocol (attached in [Supplementary Information, appendix 2](#)) was granted by the ethics committees of the National Children's Hospital, COIBI-CCSS and Universidad de Costa Rica.

2.3. Study endpoints

Primary endpoints: For efficacy the objective was to determine if there was a statistically significant difference between the two therapeutic groups regarding the development of intra-abdominal abscesses and treatment failures. For safety the objective was to determine if there was a statistically significant difference between the two therapeutic groups regarding the development of nephrotoxicity and ototoxicity.

Secondary endpoints: We also assessed if there was a statistically significant difference between the two therapeutic groups of patients with respect to body temperature, leukocyte count, C-reactive protein (CRP) serum concentration, and hospital stay.

2.4. Study protocol

One hundred patients were assigned to either regimen using computer-generated random numbers kept by the pharmacists; the blinding was not broken until the end of the study. An interim analysis was done when 40 patients were enrolled in the study to look for significant differences in efficacy and safety between the two groups. At that point there were no differences. Using a

computer-generated randomization program (<http://www.randomizer.org>), the patients were randomized into either the ODD arm, to receive 22.5 mg/kg every 24 h, or the MDD arm, to receive 7.5 mg/kg every 8 h; only the pharmacist was aware of the randomization assignment. The amikacin dose was calculated according to body weight in all cases and was not adjusted in any case.

VP (first author) was responsible for the random allocation sequence, the surgeon who performed the surgery (usually the pediatric surgical resident) enrolled the participants, and the pharmacist assigned the subjects to the intervention. Patients and care providers were kept blind to the intervention. Patients assigned to MDD received amikacin sulfate 7.5 mg/kg of body weight every 8 h as a 20-min infusion, without exceeding 500 mg per dose. Patients assigned to ODD received amikacin sulfate 22.5 mg/kg of body weight once daily over the same infusion time as MDD and not exceeding 1.5 g per dose. In the ODD group, the first amikacin dose was followed by two further doses of saline every 8 h in a volume equal to that of the corresponding amikacin dose. The color of the solution was the same and only the pharmacist who prepared the solution knew the intervention group. All study patients also received clindamycin 10 mg/kg, administered as an intravenous infusion over 20 min every 6 h. Patients with perforated appendicitis and localized peritonitis were given antibiotics for a minimum of 5 days and those with generalized peritonitis received antibiotics for at least 7 days. Antibiotic treatment beyond 7 days was administered to patients with a documented intra-abdominal abscess defined by the presence of one or more collections in the pre-rectal space, right iliac fossa, mid-abdomen, or retrovesical area, visualized by abdominal ultrasound.

2.5. Cultures

Samples of peritoneal exudates were obtained from all patients and sent for aerobic bacterial cultures. They were plated onto blood and MacConkey agar and only the predominant organism from each culture was reported. The minimum inhibitory concentration (MIC) for amikacin was determined for any bacteria grown from an intraoperative sampling, and the maximum concentration (C_{max})/MIC ratio was calculated for each isolate.¹⁵ Anaerobic cultures were not performed.

2.6. Amikacin serum concentrations

Amikacin peak and trough serum concentrations were measured on days 2, 4, 6, and 8 of therapy. After sampling, plasma was separated and frozen at -70°C until processed (within 1 month). Amikacin concentrations were determined by fluorescence polarization immunoassay (Abbott Tax; sensitivity 0.8 $\mu\text{g/ml}$).

2.7. Renal function assessment

The serum creatinine concentration was determined prior to the start of therapy with amikacin and every 48 h thereafter until its discontinuation. Any abnormal value was followed until its return to the normal range according to age. Amikacin-related renal toxicity was defined as an increase in serum creatinine ≥ 0.4 mg/dl from the basal post-rehydration value before the first dose was administered.

2.8. Cochlear function

Cochlear function was assessed according to the age of the patient. Children younger than 4 years of age were screened through oto-acoustic emissions (OAE-DP), immittance, and free-field audiometry (behavioral observational audiometry, BOA). Children over the age of 4 years were assessed with conventional

behavioral play audiometry and immittance.¹⁶ BOA and play audiometry were considered normal with thresholds ≥ 20 dB at 0.5, 1, 2, 4, 8 kHz. OAE were assessed considering the presence or absence of distortion products in the frequencies of 2, 3, 4, and 5 kHz. Absence or reduction in the noise-tone difference (NTD) with respect to baseline for the emissions was considered abnormal. All patients were tested by the same person (JM) who was unaware of the randomization. Patients had baseline tests done on day 3 of admission to the study and at a follow-up examination 6 weeks after discharge. Ototoxicity or cochlear damage was defined by sensori-neural hearing impairment predominant in the frequencies between 2 and 8 kHz. A drop of 10–15 dB hearing levels (HL) at one or more frequencies, usually at 2, 4, 6, and 8 kHz, with respect to baseline values was considered abnormal.¹⁷

All patients underwent abdominal ultrasound on days 5 and 10 after surgery in order to rule out intra-abdominal abscesses. The person who performed the ultrasound was unaware of the therapeutic regimen of each patient. Clinical success was determined by the absence of intra-abdominal collections on days 5 to 10 of therapy and an axillary body temperature ≤ 37.5 °C for at least two consecutive days, leukocyte count below 12×10^9 cells/l, and serum CRP ≤ 40 mg/l. Treatment failure was defined by persistence of an intra-abdominal abscess after 10 days of effective antibiotic therapy accompanied by fever, leukocyte count above 12×10^9 cells/l, and a serum CRP > 40 mg/l. Amikacin and clindamycin were stopped in these patients and they were successfully treated with the combination of metronidazole and ceftazidime for 7 days.

2.9. Statistical analysis

Approximately 800 patients are admitted to our hospital with a diagnosis of acute appendicitis every year. Between 300 and 350 of these children are diagnosed with perforated appendicitis, and the incidence of intra-abdominal abscesses has been estimated to be between 25% and 30% in our institution in the past. We calculated that a sample size of 100 patients would allow us to detect a reduction in the incidence of intra-abdominal abscess from 30% to 5%, assuming a power of 80% and a cut-off for statistical significance of 0.05.

The unpaired Student's *t*-test for parametric data was used to compare body temperature, leukocyte count, CRP, serum creatinine, C_{\max}/MIC , and duration of hospital stay. A two-tailed Fisher's exact test for categorical data was used to compare intra-abdominal abscess and treatment failure. Test results were calculated using SPSS version 6.0 (SPSS Inc., Chicago, IL, USA) and STATA MP version 11 (StataCorp., College Station, TX, USA).

3. Results

Fifty children were enrolled into each arm of the study between April 2005 and February 2006. The trial was closed when 100

subjects were enrolled. There were no differences in demographic or clinical characteristics between the MDD and ODD groups (Table 1). Twenty-one patients in each group had perforated appendicitis with localized peritonitis and 29 in each group had generalized peritonitis. There were no deaths during the study period. Three patients were withdrawn from the study within the first 72 h after randomization at the parents' request; the outcomes of these subjects were excluded from the analysis.

No statistically significant differences in daily body temperature between the two groups were documented. Seventy-one percent of the patients in the MDD group were afebrile by day 4 vs. 70% in the ODD group, with mean axillary temperatures of 37.3 ± 0.67 °C and 37.3 ± 0.7 °C, respectively ($p = 0.7$). Eighty-eight percent of the patients in the MDD group were afebrile by day 7 vs. 89% in the ODD group ($p = 0.8$) (Figure 1).

Leukocyte counts were similar in the two treatment groups on days 4 and 8 of treatment. Mean counts on day 4 in the MDD and ODD groups were $11.179 \pm 3.625 \times 10^9$ cells/l and $10.385 \pm 3.515 \times 10^9$ cells/l, respectively ($p = 0.2$). On day 8 they were $14.300 \pm 4.381 \times 10^9$ cells/l and $14.421 \pm 4.713 \times 10^9$ cells/l, respectively ($p = 0.9$) (Figure 2).

CRP concentrations in both groups were similar throughout the study. On day 4 of treatment the mean CRP concentrations were 64 ± 41 mg/l in the MDD group vs. 74 ± 49 mg/l in the ODD group ($p = 0.3$), and on day 8 they were 40 ± 39 mg/l in the MDD group vs. 46 ± 21 mg/l in the ODD group ($p = 0.7$) (Figure 3).

Overall 11 patients developed intra-abdominal abscesses for an incidence of 11%; this included eight patients in the MDD arm and three in the ODD arm (relative risk (RR) 2.67, 95% confidence interval (CI) 0.75–9.47; $p = 0.11$). Six patients had unresolved peritoneal abscesses after completing 10 days of amikacin and clindamycin; all of them were successfully treated with a combination of metronidazole and cefotaxime and none of them required surgical drainage. Five of these patients belonged to the MDD group and one to the ODD group (RR 5.0, 95% CI 0.6–41; $p = 0.09$). There were no differences between the study groups with respect to hospital stay; the MDD group had a mean hospital stay of 178.7 ± 72.7 h vs. 169 ± 61.3 h for the ODD group ($p = 0.7$).

There was no evidence of renal toxicity in any of the patients. On day 4 of therapy, patients in the MDD and ODD groups had a mean serum creatinine value of 0.5 ± 0.11 mg/dl ($p = 0.9$). On day 8, the values were 0.5 ± 0.17 mg/dl for the ODD group and 0.6 ± 0.1 mg/dl for the MDD group ($p = 0.2$) (Figure 4).

All patients enrolled in the study had normal baseline auditory function tests. Eighty-one patients, 40 in the MDD group and 41 in the ODD group, had follow-up examinations. Two patients, one from each therapeutic group, had a mild (20–39 dB) decrease in auditory acuity.

Regarding amikacin serum levels, the mean trough amikacin concentrations were significantly lower in the ODD regimen on days 2, 4, and 6. In this group none of the patients had trough

Table 1
Characteristics of the study patients

	ODD group (n = 50)	MDD group (n = 50)	p-Value
Age (months)	94 ± 36	98 ± 33	0.6
Gender			0.5
Male	26 (52)	30 (60)	
Female	24 (48)	20 (40)	
Weight (kg)	26.9 ± 11.2	30.6 ± 12.6	0.12
Height (cm)	122.3 ± 18.4	126 ± 16.9	0.29
Temperature (°C)	38.6 ± 0.68	38.5 ± 0.77	0.3
Leukocyte count ($\times 10^9/l$)	18.005 ± 6.123	17.172 ± 5.731	0.47
CRP (mg/l)	147 ± 91	151 ± 85	0.82
Serum creatinine (mg/dl)	0.58 ± 0.16	0.6 ± 0.13	0.5

Results are given as mean \pm SD or n (%).

ODD, once daily dosing; MDD, multiple daily dosing; CRP, C-reactive protein; SD, standard deviation.

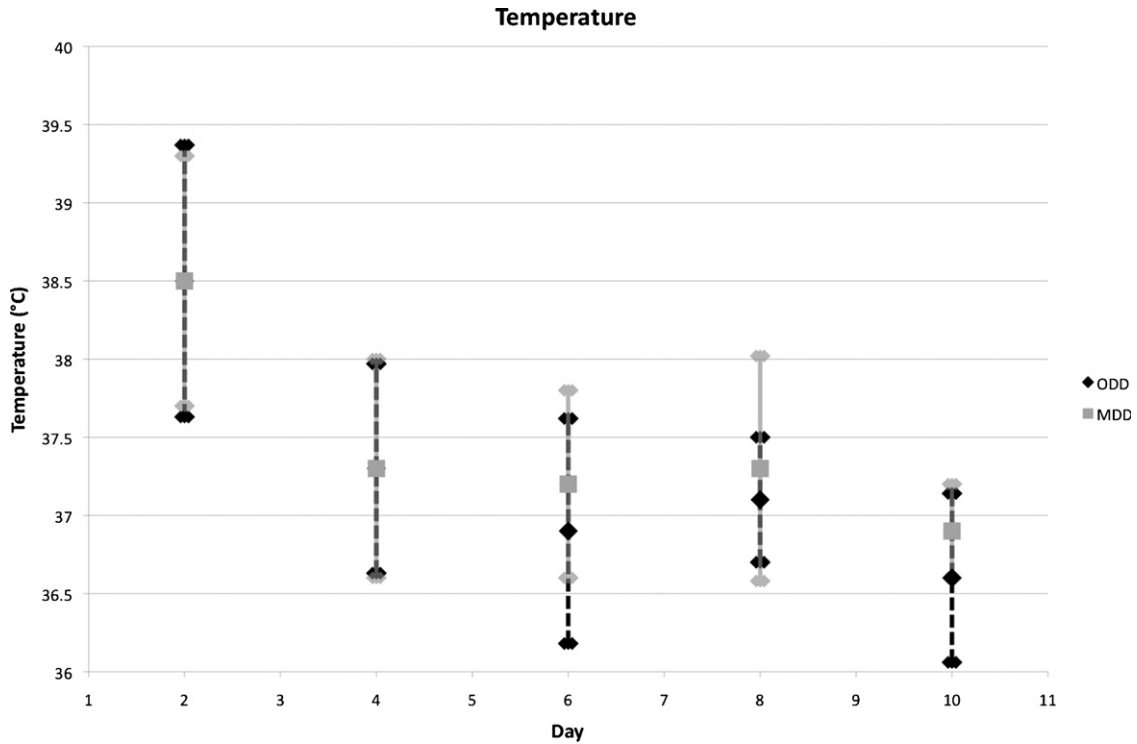


Figure 1. Median and IQR for temperature for the ODD and MDD group, Day 1 to Day 10.

amikacin concentrations higher than 5 $\mu\text{g/ml}$. Two patients on the MDD regimen had toxic trough amikacin concentrations: one had 13.1 $\mu\text{g/ml}$ on day 4 and the other 17.8 $\mu\text{g/ml}$ on day 8. Both patients had normal renal function according to serum creatinine: the first one had a trough amikacin concentration of 2.7 $\mu\text{g/ml}$ 2 days later when she finished treatment; the second patient

completed 10 days of amikacin and levels were not taken that day because he was discharged early. Mean peak concentrations were higher in the ODD regimen on days 2, 4, 6, and 8; none of the patients in this group had amikacin concentrations below 30 $\mu\text{g/ml}$ (Figure 5). $C_{\text{max}}/\text{MIC}$ was calculated for 73 patients who had positive cultures from the peritoneal cavity, 37 in the MDD group

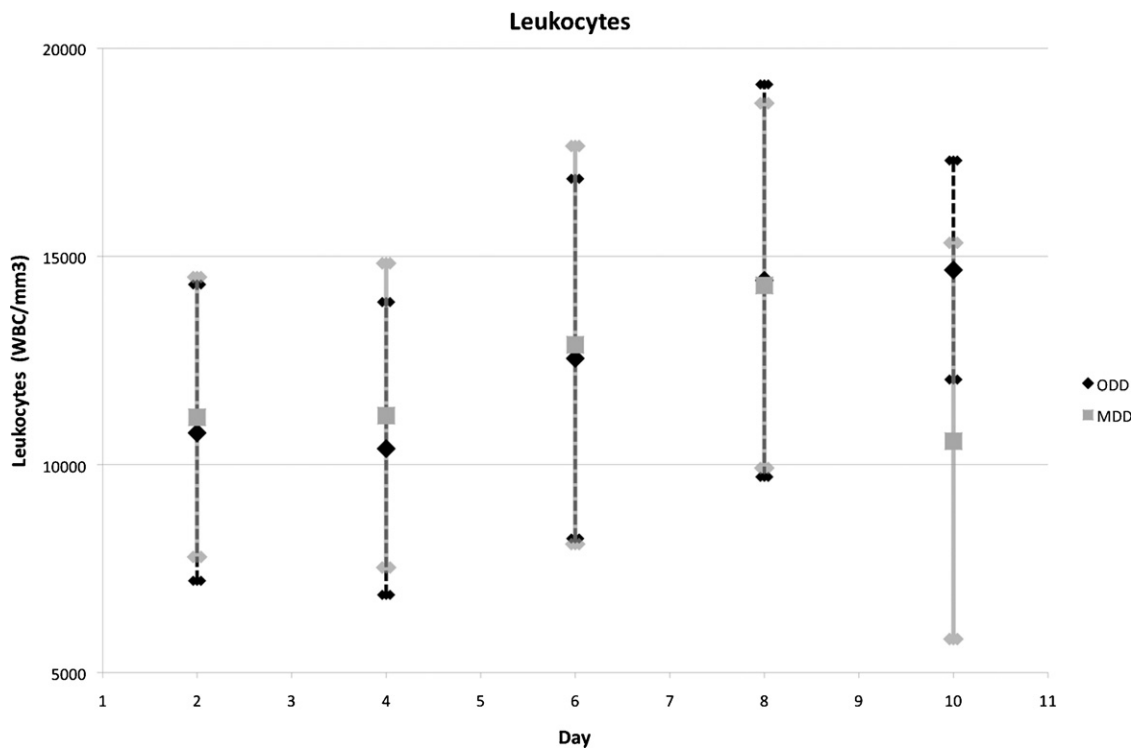


Figure 2. Median and IQR of leukocyte counts for the ODD and MDD group, Day 1 to Day 10.

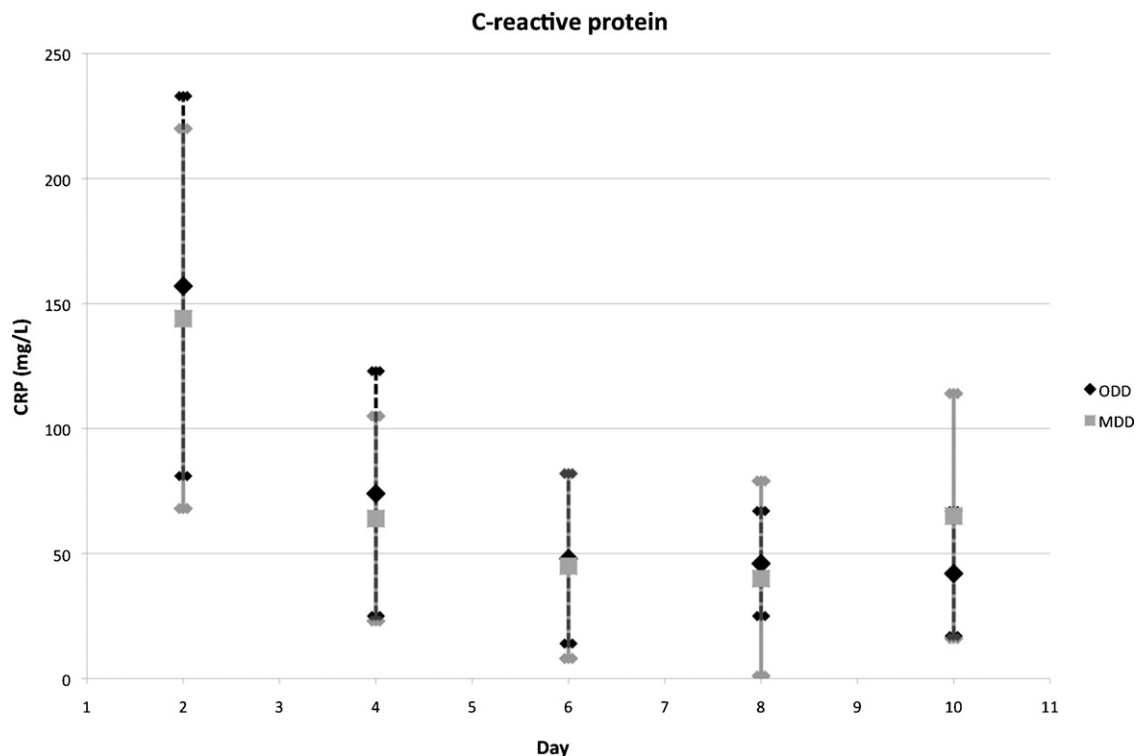


Figure 3. Median and IQR of C-reactive protein for the ODD and MDD group, Day 1 to Day 10.

and 36 in the ODD group. Patients in the MDD group had a mean C_{max}/MIC value of 9 ± 3.6 vs. 21 ± 4.7 mg for those on the ODD regimen ($p < 0.01$).

Patients from both therapeutic groups were bacteriologically comparable. Peritoneal samples from 37 patients in the MDD group had bacterial growth: *Escherichia coli* ($n = 36$) and *Pseudomonas aeruginosa* ($n = 1$). The samples from the other 13 patients had sterile aerobic cultures. Thirty-six patients in the ODD group had bacterial growth from their peritoneal samples: *E. coli* ($n = 30$), *P. aeruginosa* ($n = 3$), *Klebsiella pneumoniae* ($n = 2$), and *Citrobacter freundii* ($n = 1$); 14 of the patients had sterile aerobic cultures. *E. coli*

isolates had a MIC for amikacin of $2 \mu\text{g/ml}$ in 63 patients and of $4 \mu\text{g/ml}$ in three patients. *P. aeruginosa* isolates had a MIC for amikacin of $2 \mu\text{g/ml}$ in three patients and of $8 \mu\text{g/ml}$ in one patient. *K. pneumoniae* and *C. freundii* isolates had a MIC for amikacin of $2 \mu\text{g/ml}$.

4. Discussion

This study, carried out in pediatric patients with perforated appendicitis, provides additional evidence for the efficacy and safety of ODD of aminoglycosides compared to MDD. We chose to

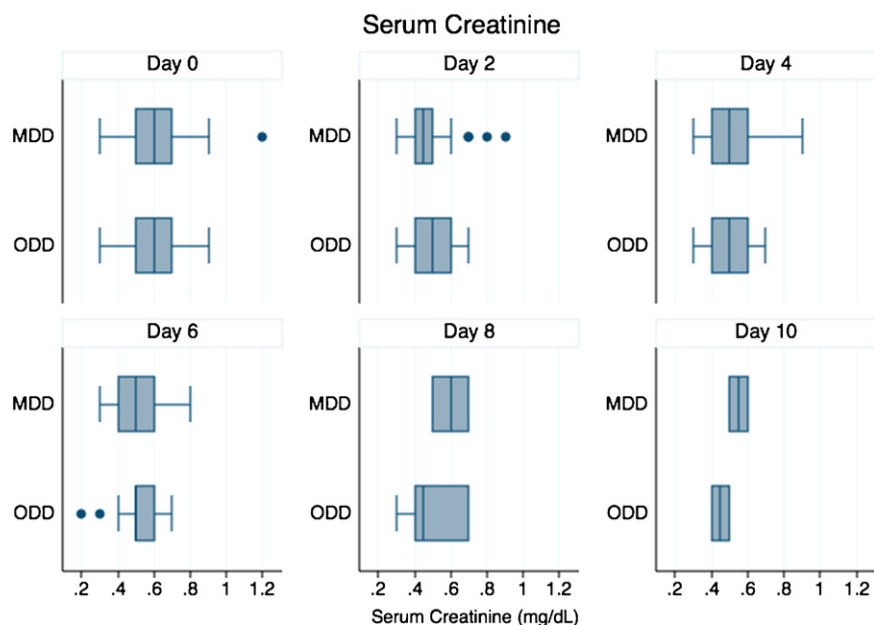


Figure 4. Median and IQR of serum creatinine for the ODD and MDD group, Day 1 to Day 10.

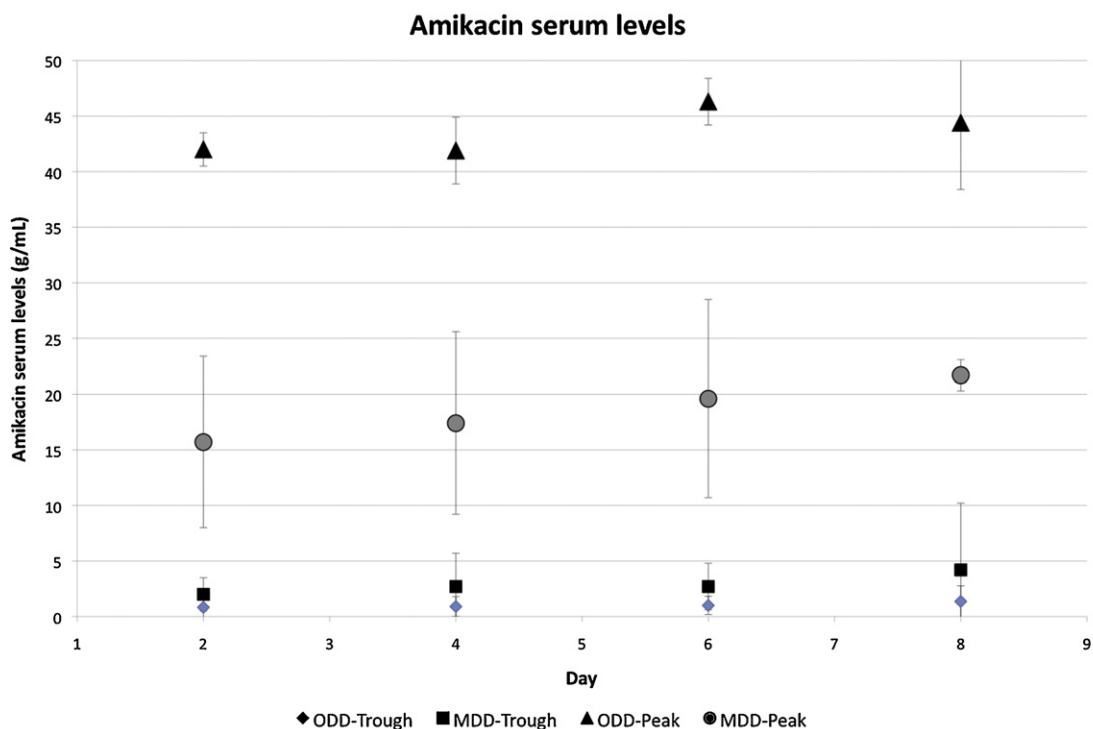


Figure 5. Median and IQR of amikacin serum levels for the ODD and MDD group, Day 2 to Day 8.

conduct the study in children with perforated appendicitis because it is the most common abdominal surgical emergency in pediatric patients,¹⁸ and since all patients with a ruptured appendix are undoubtedly infected, it is possible to evaluate the true efficacy of each regimen.

Our study did not find any significant differences in the clinical evolution between the two groups of patients, i.e., body temperature, leukocyte count, and serum CRP concentration. The most clinically pertinent finding of this study was the lower incidence of intra-abdominal abscesses in patients on the ODD regimen. This might be explained by the fact that these patients had significantly higher C_{max}/MIC and it is well known that the bactericidal action of aminoglycosides is concentration- and area under the curve (AUC)-dependent.¹⁹ Patients on the MDD regimen had a higher rate of therapeutic failures in accordance with previous studies that have demonstrated a direct relationship between outcome and pharmacokinetic–pharmacodynamic (PK/PD) parameters.^{20–23}

Of critical consideration is that most health centers in developing countries cannot afford to measure aminoglycoside serum concentrations on a regular basis due to limited resources. Although our study did not show a statistically significant difference between the two regimens with regard to efficacy, there was a trend towards a lower incidence of intra-abdominal abscess formation and therapeutic failure with the ODD regimen. An overly ambitious effect size estimation may have led to inadequate power for our study, and may explain our failure to attain statistical significance in our primary endpoint analyses. Our results do suggest that this is a safe regimen. Although some clinicians^{24,25} consider intraoperative abdominal cavity cultures of no value in patients with perforated appendicitis, we routinely perform aerobic cultures from all samples obtained during surgery. In this study, the two groups of patients were comparable with respect to the aerobic isolates and their susceptibility patterns to aminoglycosides, namely gentamicin and amikacin.

Also of clinical and standard of care importance, we found that patients in the MDD group had mean peak serum amikacin levels that did not reach therapeutic concentrations, contrary to our previous assumption; this finding can be explained by the fact that patients with peritonitis have a much greater volume of distribution.⁹ At our hospital we have routinely treated these patients with amikacin at a dose of 7.5 mg/kg administered every 8 h with the aim of reaching peak levels of at least 25 µg/ml and trough levels of less than 5 µg/ml.²⁶ Also of note is that two patients with normal renal function according to serum creatinine in the MDD group had trough amikacin levels above the maximum accepted concentration.

While some debate exists on the ideal method for monitoring renal toxicity in patients treated with aminoglycosides, in our study we could not demonstrate any case of primary nephrotoxicity in patients as defined by Kumana and Yuen,²⁷ neither could we find any significant difference when we compared serum creatinine levels between the two groups of patients.

Our study, like others,²⁸ showed a similar low incidence of ototoxicity in the two therapeutic groups. Although the exact mechanism of this toxic effect is unknown, it has been suggested that ototoxicity occurs mostly in patients with impaired renal function and with the concomitant use of other nephrotoxic drugs that elevate aminoglycoside serum concentrations and enhance their cochlear toxicity.²⁹ None of our patients had these predisposing conditions, which may account for the low incidence of ototoxicity in our trial.

To summarize, the results of this trial show that ODD of amikacin is an effective and equally safe regimen in comparison to MDD. Also, the ODD regimen provides more appropriate PK/PD parameters than the MDD. This study was not designed to address a cost–benefit analysis of MDD vs. ODD. However, one could hypothesize that the ODD regimen might reduce the cost of antibiotic treatment in patients with perforated appendicitis, based on the fact that this regimen implies a reduction in the cost of preparation, administration, and the total amount of drug used for each patient.³⁰

Acknowledgement

We wish to express our gratitude to the anonymous reviewers whose comments helped to improve the presentation of this article.

Disclaimer: MH was not paid for his assistance on this manuscript. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of their respective institutions.

Conflict of interest: The authors declare no conflicts of interest, personal or financial.

Funding: This study was partially supported by the Center for Postgraduate Studies (CEP) of the University of Costa Rica, San José, Costa Rica. The study sponsors had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2011.04.012.

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