Official Study Title: Once-Daily versus Thrice-Daily Clindamycin for the Treatment of Septic Abortion: a single-center randomised controlled trial

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INTRODUCTION

Obstetric infections are very frequent, especially in developing countries, as a consequence of the practice of unsafe abortion. In these countries, approximately five million women are hospitalized each year due to complications from induced abortions, wh ich is equivalent to a rate of 5-7 per thousand women (1).

Abortion remains one of the main causes of maternal death in developing countries. According to the World Health Organization, it is estimated that 1 in every 8 maternal deaths is due to complications from illegal abortion (2). Infected abortion plays an i mportant role in maternal morbidity and mortality (3). The diagnosis of septic abortion should be considered when a woman of reproductive age presents with a missed period, vaginal bleeding, accompanied by abdominal pain and fever (4).

Early diagnosis and effective treatment of endometritis are essential to prevent the progression of the infection. Among the possible interventions, uterine evacuation by manual vacuum aspiration and the use of antibiotics for septic abortion are effective and well-documented. If there is a delay in initial therapy, the infection can progress to bacteremia, peritonitis, pelvic abscess, septic pelvic thrombosis, disseminated intravascular coagulation, septic shock, renal failure, and death (3).

At the Hospital de Clínicas de Porto Alegre (HCPA), the routine of the Gynecology and Obstetrics Service recommends the use of intravenous antimicrobials (Gentamicin and Clindamycin) before starting curettage in cases of infected abortion (5). The efficacy and effectiveness of aminoglycosides in gynecological and obstetric infections have been extensively evaluated in the scientific literature (6 -8), with gentamicin and clindamycin being the main drugs used (8). Currently, the regimen recommended by the Min istry of Health is 600 to 900mg of Clindamycin every 6 or 8 hours intravenously for 7 to 10 days and 1.5mg/Kg/dose of gentamicin every 8 hours intravenously for 7 to 10 days (4); our group, however, has shown that there is an equivalence in cure rates if t he antibiotic is used for 48 hours after a good clinical response or for 10 days (9).

Due to its pharmacodynamic characteristics and its adverse effects, the definition of the best administration interval for gentamicin has been the subject of several studies that have shown that single-dose administration is the best way to avoid its delet erious effects (such as adaptive resistance and toxicities) and to enhance its bactericidal effect (in addition to maintaining the post-antibiotic effect for a longer time) (10, 11). Furthermore, single-dose administration is directly and indirectly less c ostly for health services, as it not only requires a smaller amount of medication but also results in less need for care from the nursing staff (11).

In 1989, Plaisance et al. demonstrated that Clindamycin could be prescribed in a 12/12 hour dose, with inhibitory serum levels for the tested bacteria being similar to those of the

fractionated doses of 6/6 hours (12). In 2003, Livingston et al. published the results of combined gentamicin and clindamycin in a single daily dose for cases of post-cesarean endometritis. The administration of Clindamycin was different in that it was a single dose of 270 0 mg per day, different from the fractionated dose of 6/6 hours, or 8/8 hours, with cure rates of 82% (45 successes out of 56 cases) in the single daily dose (13). The etiology of postpartum endometritis is similar to that found in infected abortion (14, 15), but there is little information regarding the use of a single daily dose in this disease.

A retrospective study, recently conducted by our group, showed that patients with infected abortion treated with a single dose of Clindamycin had cure rates of 98% (95% CI - 95 to 99%), suggesting an equivalence between the single daily dose and the conventional treatment of 3 daily doses (16).

It is necessary to emphasize that, being a retrospective study, the results found are not substantial evidence to support the use of single-dose Clindamycin in clinical practice. Therefore, a prospective study would be the most appropriate to address this.

RATIONALE

Few studies demonstrate the equivalence of using a single daily dose of Clindamycin compared to fractionated doses of the same. The single daily dose regimen is more convenient, can be administered in a day hospital setting, involves less handling by the nursing staff in the preparation process, uses fewer materials, and avoids hospital admission. It also has financial advantages over fractionated doses. Therefore, the present study is justified as it is more suitable for confirming previous studies and the hypotheses generated to date.

OBJECTIVES

To verify the equivalence of using Clindamycin once a day versus 3 times a day on the cure rates of infected abortion.

HYPOTHESES

The percentage of clinical cure with traditional treatment (Ps) is greater than or equal to the percentage of cure with the alternative treatment + 2%.
H0: Ps >= Pn + 2
The percentage of clinical cure with traditional treatment (Ps) minus 2% is less than the percentage of cure with the alternative treatment (Pn)
Ha: Ps– 2% < Pn

Variables

1. Traditional treatment group (Clindamycin 3x a day)
2. Alternative treatment group (Clindamycin 1x a day)

3. Clinical improvement (present or absent), defined as the absence of fever (<= 37.7ºC), normalization of the white blood cell count (<12,000 total leukocytes), tolerating oral intake, and walking without difficulty. As previously described in the literature (9).

MATERIALS AND METHODS

Study Design

A randomized, prospective, double-blind, two-arm study that will follow the CONSORT guidelines (17).

Geographic and Temporal Scope

The study will be conducted with patients treated in the emergency department of the Hospital de Clínicas de Porto Alegre (HCPA) by Dr. Ricardo Savaris's team. A period of 24 months will be allowed for data collection (approximately 4 patients per month).

Inclusion Criteria

All patients who come to the HCPA emergency department with a clinical diagnosis of infected abortion and have an indication for treatment with Clindamycin. The diagnosis of infected abortion will be the same as previously used by our group (9). In summary , the presence of one of the criteria below in a pregnancy of less than 20 weeks associated with a suspicion of ovular infection:

1. History of intrauterine manipulation with contaminated objects.
2. Vaginal secretion with a foul odor.
3. Presence of pus flowing from the cervix.
4. Signs of peritoneal irritation.
5. Leukocytosis (> 14,000 leukocytes/mL).
6. Warm extremities, thready pulse, and tachycardia (HR > 110 bpm).
7. Cyanosis and/or pallor.
8. Tachypnea (RR > 30 rpm).
9. Arterial hypotension (SBP < 90mmHg).
10. Oliguria.
11. Hyperthermia (>= 37.8ºC).

Exclusion Criteria

All patients who meet the following criteria will be excluded:

1. Do not wish to participate in the project.
2. Used antimicrobials prior to admission (within a 1-week period).
3. Are allergic to Clindamycin or gentamicin.

Execution

Eligible patients for the study will be invited to participate in the research at the time of their admission to HCPA to undergo uterine curettage. After reading and signing the informed consent, the patients will undergo a standardized interview (Appendix 1), and immediately after the initial interview, the patient will be randomized.

Randomization

Patients will be randomly allocated to treatment with Clindamycin 3 times a day or Clindamycin once a day, using a computer-generated list with random treatments grouped in blocks of 4 combinations. The randomization sequence will be obtained from sealed, sequential envelopes held by the HCPA emergency department pharmacy. This way, the researcher will not have prior access to the treatment sequence. The Emergency Service pharmacy will perform the randomization and prepare the medication as part of the routine of the HCPA Gynecological Emergency Unit.

The treatment will be blinded for the patient, as the administration of the drug causes specific effects that will let the patient know which medication she is using.

Treatment

The therapeutic regimen will consist of:

- **Standard treatment (Ps):** Clindamycin (900mg intravenously every 8 hours, diluted in 250 mL of 0.9% saline solution (SS)). Gentamicin 240 mg will be added to the first bag of SS.
- **Alternative treatment (Pn):** Clindamycin (2700mg) + gentamicin (240 mg) diluted in 250 mL of 0.9% SS. Two additional bags of 0.9% SS will be administered at 8 -hour intervals as a placebo.

Treatment will be continued until 48 hours of good clinical status is completed, defined as the absence of fever, decreased vaginal bleeding, minimal or no pain (VAS < 4), normal white blood cell count, tolerating food and water, and walking normally.

Follow-up

All women included in the study will be re -evaluated up to 7 days after hospital discharge as part of the gynecological emergency routine when they return to receive the results of the anatomopathological examination.

OUTCOMES

The following outcomes will be determined:

1. **Clinical improvement** up to hospital discharge in terms of the number of days of hospitalization, and treatment -related complications.
2. **Treatment failure:** will be considered as the persistence of fever (>=37.8ºC) during hospitalization, worsening of abdominal pain, persistence of bleeding, the need to change Clindamycin due to therapeutic failure, or the need to add other intravenous or oral antibiotics.
3. **Return to the emergency department** within 7 days after discharge due to fever (Temp. >=37.8ºC) persistence of uterine or adnexal pelvic pain, persistence or increase of uterine bleeding, or hospital admission for abortion -related problems.

4. The presence of a urinary tract infection or candidal vaginitis, or failure due to the persistence of retained products of conception will not be considered as therapeutic

failure.

SAMPLE SIZE

The sample size was calculated as a non-inferiority binary clinical trial, using the formula proposed in the literature (18). According to data obtained in a retrospective study by our group (16), we expect the estimated clinical cure rate to be 99% (95% C I - 95% to 99%) in the group with 3 daily doses and 100% (95% CI - 99% to 100%) in the experimental treatment. For a non-inferiority study, using a power of 90%, an alpha error of 5%, and a lower non - inferiority limit of 2%, 95 cases will be needed in each group. Considering some losses, the study will continue until 100 cases are completed in each arm.

STATISTICAL ANALYSIS

The data will be analyzed by intention - to - treat and per - protocol. The definition of intention - to - treat is based on the criteria suggested in the literature (19). The statistical analysis used will be the Student's t - test to compare the difference in means and proportions with a confidence interval, and the chi - square test for nominal data.

ETHICAL ASPECTS

This study will be submitted to the ethics and research committee of HCPA.

Information Ownership
The privacy and confidentiality of the patients will be preserved. Only general data will be disclosed.

REFERENCES

1. Singh S. Hospital admissions resulting from unsafe abortion: estimates from 13 developing countries. Lancet 2006;368:1887-92.
2. Ahman E, Shah IH. New estimates and trends regarding unsafe abortion mortality. Int J Gynaecol Obstet 2011;115:12-16.
3. Stubblefield PG, Grimes DA. Septic abortion. N Engl J Med 1994;331:310-4.
4. Brasil. Ministério da Saúde. [Infected abortion]. In [Maternal urgencies and emergencies. guide to diagnosis and management of the risk of maternal death], 2ed. Editado por Brasília, Ministério da Saúde/FEBRASGO, 2000, p 13-28.
5. Savaris R. [Abortion]. In Rotinas em Obstetrícia, 6ed. Editado por Freitas FM, Costa SMH, Lopes JG, Magalhães JA. Porto Alegre, Artmed, 2011, p 97-109.
6. Del Priore G, Jackson-Stone M, Shim EK, Garfinkel J, Eichmann MA, Frederiksen MC. A comparison of once - daily and 8-hour gentamicin dosing in the treatment of postpartum endometritis. Obstet Gynecol 1996;87:994-1000.
7. Hemsell DL, Martens MG, Faro S, Gall S, McGregor JA. A multicenter study comparing intravenous meropenem with clindamycin plus gentamicin for the treatment of acute

gynecologic and obstetric pelvic infections in hospitalized women. Clin Infect Dis 1997;24 Suppl 2:S222-30.
8. French LM, Smaill FM. Antibiotic regimens for endometritis after delivery. Cochrane Database Syst Rev 2004;CD001067.
9. Savaris RF, de Moraes GS, Cristovam RA, Braun RD. Are antibiotics necessary after 48 hours of improvement in infected/septic abortions? A randomized controlled trial followed by a cohort study. Am J Obstet Gynecol 2011;204:301.e1-5.
10. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39:650-5.
11. Rao SC, Srinivasjois R, Hagan R, Ahmed M. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev 2011;CD005091.
12. Plaisance KI, Drusano GL, Forrest A, Townsend RJ, Standiford HC. Pharmacokinetic evaluation of two dosage regimens of clindamycin phosphate. Antimicrob Agents Chemother 1989;33:618-20.
13. Livingston JC, Llata E, Rinehart E, Leidwanger C, Mabie B, Haddad B et al. Gentamicin and clindamycin therapy in postpartum endometritis: the efficacy of daily dosing versus dosing every 8 hours. Am J Obstet Gynecol 2003;188:149-52.
14. Moberg PJ, Gottlieb C, Nord CE. Anaerobic bacteria in uterine infection following first trimester abortion. Eur J Clin Microbiol 1982;1:82-6.
15. Soper DE. Postpartum endometritis. Pathophysiology and prevention. J Reprod Med 1988;33:97-100.
16. Giugno CS, Silva AL, Fuhrich DG, Rabaioli PS, Goncalves KG, Sartor NC et al. Daily dose of clindamycin versus standard divided doses in obstetrical and gynecological infections: A retrospective cohort study. Int J STD AIDS 2013
17. Grimes DA. The "CONSORT" guidelines for randomized controlled trials in Obstetrics & Gynecology. Obstet Gynecol 2002;100:631-2.
18. Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials 1982;3:345-53.
19. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 1999;319:670-4.