Chloramphenicol Wound Infection Prophylaxis

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Introduction

Chloramphenicol ointment is FDA-indicated for the treatment of bacterial conjunctivitis. However, since this antibiotic is available as a topical formulation, there may be other practical uses for this medication. Before this study was performed, many of the health practitioners involved had already previously used chloramphenicol ointment on sutured wounds as prophylaxis for infection.

This prospective randomized controlled study seeks to be the first analysis to determine the effectiveness of this prophylaxis treatment following minor skin surgery. The participants were patients of one of fifteen doctors at three private general practices in Mackay, Queensland. Nurses invited patients who presented for minor skin excisions to take part in the study. Exclusion criteria were the use of oral antibiotics, the indication of oral or topical antibiotics postoperatively, the use of immunosuppressive drugs, excision of sebaceous cyst, history of allergy to any ingredient in Chloromycetin® ointment, and personal or family history of aplastic anemia.

Five hundred nine patients were randomized to receive the commercially available Chloromycetin® ointment with 10 mg/g chloramphenicol and 505 were randomized to the placebo group and were to receive paraffin ointment. The doctors applied sufficient amounts of the respective ointment relative to the sutured wound following surgery. The primary outcome measure was the incidence of infection. The care of all patients was similar regardless of treatment. All patients received written instructions on postoperative wound care. Participating general practitioners got together to develop guidelines to ensure that excisions were managed in a standardized manner. All participating patients got written instructions on postoperative wound care and were asked to take their dressing off after 24 hours and to avoid using antiseptics.

Doctors and nurses evaluated patients based on the developed scale on the pre-arranged day for suture removal or sooner if warranted by suspected infection. The wound scale was designed as a combination of the CDC's National Nosocomial Infection Surveillance System, literature research, and the investigators' clinical experience. With a projected infection rate of 10%, the investigators decided that an absolute decrease in incidence of infection of 5% would be clinically significant.

Element	Criteria	Comments
Study Design Assessment	Is the design appropriate to the research question? Is the research question useful?	Yes. This is a study dealing with treatment, and the appropriate study design for a therapeutic intervention is a prospective, randomized placebo-controlled, double-blind trial. The research question—"To determine the effectiveness of a single application of topical chloramphenicol ointment in preventing wound infection after minor dermatological surgery"—is useful.
Internal Validity Assessment	Can bias, confounding or chance explain the study results?	Yes. If patients' treatment group assignments were revealed to them inadvertently, the "placebo effect" may affect wound healing based on the patients' beliefs of whether the chloramphenicol or lack of would be effective infection prophylaxis. There are many exclusion criteria but the inclusion criteria are vague, especially of what is considered a "minor skin procedure." ***THREAT:*** It is subjective how much ointment is necessary to cover a wound. A particular amount of ointment (with or without chloramphenicol) may be more effective in preventing infection than another. This would vary the amount of drug present as well in the chloramphenicol dosing.
Selection Bias	Are groups truly randomized (concealment of allocation strategies, similar group characteristics, avoids potential for anyone affecting assignment to study arm, etc.)?	Nurses in the participating medical centers initially selected the patients for enrollment as well as assisted with collecting the demographic information and medication history necessary for the computer randomization process. Computer-generated random numbers and opaque sealed envelopes were used to randomize patients. Even though this process can be manipulated, the longitudinal involvement of the nurses would make the concealment of the treatment group placement more successful. Only the primary investigator was aware of the identity of the coded ointments. Practice nurses and doctors assessing outcome were blinded to the allocation of intervention and control groups. ***THREAT:*** There were differences at baseline such as 71.7% of the intervention group were diagnosed with non-melanoma skin cancer or solar keratosis compared with 65.1% in the control group. Inadequate data were collected on suture size and occupation, and the prevalence of diabetes and other medically-important conditions was probably understated.

Performance Bias	Has double-blinding been successfully employed? Are there any other performance biases such as differences between groups, except for what is under study?	The study was double-blinded and placebo-controlled. Only the primary investigator knew the identity of the coded ointments. Consensus could not be reached about skin preparations, so normal saline was used in one center and chlorhexidine at two centers. The intervention and placebo both used an ointment base of soft white and liquid paraffin but the treatment Chloromycetin® ointment had 10 mg/g chloramphenicol and plastibase 30W. To properly evaluate the effectiveness of chloramphenicol, no antibiotic, anti-infective, or antiseptic agents were allowed during the course of the study. This included topical application of ethyl alcohol or antiseptic washes. ***THREATS:*** • The proportions of the paraffin excipients between the two ointments may not be the same. It is unknown if plastibase 30W has any anti-infective properties. • The authors state that the placebo ointment was not completely identical to the ointment base. They do not remark if this was likely to be apparent in practice. • The authors note that there has been no published evidence that using normal saline compared to chlorhexidine for skin preparation makes any difference to infection rates; however this difference could possibly affect results. • The standard length of excision, mean number of days before removal of sutures and the difficulty of the procedure were recorded. However, even though these factors may all affect the likelihood of infection, any association to infection rate was not assessed. • The incidence of infection can be changed by the technical expertise of the health provider (i.e. using a sufficient amount of ointment and sterile technique with forceps application of ointment).
Attrition Bias	Are there any missing data points?	***THREAT:*** Twenty one patients in each group were lost to follow-up. This left 488 out of 509 (95.9%) of the intervention group and 484 out of 505 (95.8%) of the control group to be analyzed. This may cause an underreported rate and severity of infection.
Assessment Bias	Are assessors blinded? What is the likelihood of findings due to chance? Is there statistical significance or power analysis? Intention-to-treat analysis? Modeling with use of reasonable assumptions?	Doctors and nurses were unaware of which patients were in the treatment or placebo group provided the confidentiality of the patient allocation and blinding was maintained. It was not mentioned whether the individuals who performed the statistical analyses were blinded. The principle researcher collaborated with the doctors and nurses in one workshop to provide the initial training and ensure that record-keeping was similar at all practice sites. Results and percentages were presented with 95% confidence intervals. P values were based on cluster sampling from the 15 different practitioners and respective patient outcomes. Participating doctors were the primary sampling unit and the survey commands of Stata were applied. ***THREATS:*** • The 3 practice sites did not reach a consensus on what to use for skin preparation, so one center used normal saline while the others used chlorhexidine. • The diagnosis of infection was subjective. Although the researchers developed their own wound assessment scale, they could not confirm the intra- and inter-practice reproducibility of the measurement and documentation procedures. • One of the chosen clinics was a designated skin cancer clinic, which may have different criteria for infection based on their scope of practice as well as different patient demographics. • The patients lost to follow-up may have required urgent medical attention elsewhere. Therefore, the incidence of infection may be under-reported. The investigators did not perform an ITT analysis, but did look at the robustness of the results. They stated that if all 21 patients who were lost from the intervention group had developed an infection, the infection rates would have been similar to the control group (10.4% intervention, 11% control). This sensitivity analysis shows that though unlikely, the chloramphenicol treatment may have lost its advantage as being statistically significant at reducing incidence of infection if all 21 intervention group patients lost to follow-up had become infected.
Usefulness Assessment	Is there a clinically significant area and sufficient benefit size?	The authors assessed effectiveness because this study was conducted in multiple Australian hospitals. Although the results were statistically significant, the chloramphenicol did not reduce the incidence of infection enough to be clinically significant. The relative risk reduction was 40% and the absolute risk reduction was 4.4%, which was less than the pre-set 5% needed to be clinically significant. The number needed to treat was 22.8. The application of chloramphenicol would probably not produce a meaningful benefit in settings where the infection rate is already low.
External Validity	How likely are research results to be realized in the real world considering population and circumstances for care?	These results can be applicable to a very specific population: patients who are to have a skin incision procedure in a medical practice and who have reliable healthcare conducive to follow-up monitoring of wound healing. ***THREATS:*** • Chloramphenicol cannot be used in patients with larger wounds because the amount needed to cover the affected area may cause systemic toxicity. • The author did not define "minor skin excision" so there are no specific criteria available on who qualifies for treatment based on this study.

Patient Perspective	What are the benefits, risks, and costs to patients? Other alternatives? Is there potential for adherence issues or drug abuse/ dependency issues? How likely are patients to be satisfied with this treatment?	These patients should not be on concurrent antibiotic therapy to allow for better evaluation of chloramphenicol side effects. They should not have excessive skin irritation or burns prior to use. It may be useful to patients who may not be able to provide sufficient wound care. Costs for application and co-pays for doctor visit and follow-up must be considered. Since this is a one-time application, adherence is less of a problem, but it is important to abstain from bathing for 24 hours and to take care of the wound appropriately. The area may not be covered for 24 hours as well, so it may damage clothing or cause mild discomfort from the consistency of the ointment. ***THREAT:*** There is the possibility of allergic contact dermatitis or future resistance to chloramphenicol.
Provider Perspective	How likely is the healthcare provider to accept and apply this treatment? Is this FDA approved, affordable, and easily accessible?	Chloramphenicol is not FDA-approved for wound infection prophylaxis. Sterile technique is probably a more important factor in preventing infections. Patients would need to return to see if infection occurred and if other treatment is needed. ***THREAT:*** No cost data is available for chloramphenicol and it is not available in all offices because it is usually used for ophthalmic purposes. It is not commercially available in the United States.

Authors' Results & Conclusions

The authors concluded the prophylaxis with chloramphenicol ointment was statistically significant, but not clinically significant in reducing the rate of infection. It was unknown whether the ointment base itself had antibiotic properties. The formulation of the placebo was a best attempt at duplicating the Chloromycetin® ointment without chloramphenicol. The incidence of infection for the intervention was lower than that of placebo (6.6% vs 11.0%, $p = 0.10$) but the absolute risk reduction was 4.4%, which is less than the 5% needed to be clinically significant. The number needed to treat with chloramphenicol was 22.8. While the infection rate was lower, there was no statistical difference between the amount of erythema or infection as evidenced by the wound score ($p = 0.253$). Many of the patients with infected wounds with discharge were found to have Staphylococcus aureus infections (23 out of 24 cultured infections), most cases of which were benzylpenicillin resistant. *Pseudomonas aeruginosa* was cultured from a control group patient.

Reviewers' Conclusion

Infection from minor dermatological procedures can range from being an inconvenience (delayed healing, additional medical visits, and etc.) to causing irritation and pain. Chloramphenicol ointment was studied to see if it could be a useful preventative measure applied post-operatively. While this ointment has been used in the past off-label for this indication, this is the first study to examine the effectiveness of this intervention.

Many aspects of the trial are subject to interpretation. The first ambiguous area is how much ointment is needed to cover the wound. This amount may vary from just enough for a thin layer to a little more in case the clothing and movement of the patient removed some from the affected area. Next, the incidence of infection can vary depending on the size of the wound, location of the wound, and how much friction or movement the affected area may undergo. Finally, the criteria for infection may be different for each researcher. While this problem may be addressed by the cluster sampling approach and the common wound assessment scale, it still has the opportunity to skew the results.

Other factors may have altered the study other than differences at baseline. The preparation for the procedure was with normal saline which would not kill the majority of the normal flora. After the incision and evaluation, it was found that the rate of infection was 11% (more than five-fold greater than a normally acceptable 2%) in the control group. This increased risk might be accounted for by the use of normal saline over ethyl alcohol or other more trusted topical antiseptics. While both groups at the institution that used normal saline were treated in the same manner, this increased risk of infection can also be attributed to the integrity of the skin before the procedure or the prior level of pathogens on the skin, factors that were not accounted for. Also, some patients were lost to follow up who may have received medical attention elsewhere due to infection.

Chloramphenicol ointment as prophylaxis may be an option for high risk patients undergoing minor dermatological surgery. Since it did not reduce infection by a clinically significant margin of 5%, it would not be recommended for all future wound infection prophylaxis. In addition, some people use antibiotics or have a wound too large to consider the use of a topical antibiotic due to risk of systemic side effects. Healthcare insurance coverage would be helpful for patients who decide to undergo this treatment due to the necessary doctor follow-up visits. This study was performed in Australia which has a universal healthcare system for better collaboration of health services. A clinical trial in the United States to reproduce this procedure may not be as feasible due to the American healthcare structure. Aseptic technique and attention to detail with normal infection control would likely provide a greater decrease in the incidence of infection than the procedure used in this chloramphenicol study.

This investigation has multiple confounding factors that hinder recommending routine wound infection prophylaxis with chloramphenicol. Other studies may be necessary to elicit a more definite conclusion about the treatment effectiveness.

Overall Grade: B-U = Possibly Useful.

About the Authors & Guest Editors

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Dr. Michael E. Stuart and Sheri A. Strite, MS of Delfini Group, LLC are experts at systematic literature reviews. The chart template is adapted from "Delfini Group, LLC. Short Critical Appraisal Checklist: Updated 02/19/08". For more information, visit www.delfini.org.

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