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A systematic review and meta-analysis of antibiotic prophylaxis in skin graft surgery: A protocol

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ABSTRACT

Introduction: There is little evidence-based guidance on the use of prophylactic antibiotics in skin surgery; whilst antibiotics may protect against surgical site infections (SSI), they have associated side effects, increase the risk of adverse events, and can propagate antibiotic resistance. We present a protocol for a systematic review to establish whether the benefit of prophylactic antibiotics overrides the risk, for patients undergoing autograft surgery.

Methods: The systematic review will be registered a priori on researchregistry.com and will be conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). A search strategy will be devised to investigate 'skin graft surgery and use of antibiotics'. The following electronic databases will be searched, 1979–2018: PubMed, MEDLINE®, EMBASE, SCOPUS, CINAHL, PsychINFO, SciELO, The Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effect (DARE), the Cochrane Methodology Register, Health Technology Assessment Database, the NHS Economic Evaluation Databases and Cochrane Groups, ClinicalTrials.gov, Current Controlled Trials Database, the World Health Organisation (WHO) International Clinical Trials Registry Platform, UpToDate.com, NHS Evidence and the York Centre for Reviews and Dissemination. Grey literature will be searched. All comparative study designs reporting on the use of antibiotics in skin graft surgery will be considered for inclusion, namely randomized controlled trials (RCTs). Two trained independent teams will screen all titles and abstracts, followed by relevant full texts, for eligibility. Data will be extracted under standardized extraction fields into a preformatted database. Note will be made of the indication for skin graft surgery (traumatic, congenital, malignant, benign), the graft site (head & neck, trunk, upper extremities, lower extremities), type of skin graft (split thickness, full-thickness). The primary outcome will be occurrence of SSI at the donor and/or recipient sites. Secondary outcomes, if reported, will include: length of hospital stay, revision surgery required, cost of medical care, time to wound healing and cosmetic outcome.

Ethics and dissemination: The systematic review will be published in a peer-reviewed journal and presented at national and international meetings within fields of plastic, reconstructive, and aesthetic surgery. The work will be disseminated electronically and in print. Brief reports of the review and findings will be disseminated to interested parties through email and direct communication. The review aims to guide healthcare practice and policy.

1. Introduction

Skin grafting involves the surgical removal of skin from a donor site, either an autograft (from the patient's own body) or an allograft (another individuals' body), and transferring it to a new area

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where the skin is defective or has been removed [14]. Skin grafts have many indications, from trauma to oncology, and are performed by plastic and dermatological surgeons all over the world [1]. Skin grafts used following Moh's microsurgery for skin cancer can help prevent infection at the site of previous surgery by acting as an intact skin barrier (1). In addition, skin grafts can dramatically improve the cosmesis of a defect, particularly full-thickness-skin grafts on areas of high aesthetic value such as the face, and thus substantially improve patient quality of life (3).

One dreaded outcome of skin graft surgery is surgical site infection (SSI) of the grafted skin. SSIs can be disastrous; in the worst scenarios SSIs lead to systemic infection and complete non-take of the graft which can leave the patient at risk of further infection due to having an incomplete skin barrier and the need for further surgery to replace the graft (4). To prevent this, many surgeons opt to give their patients antibiotics prophylactically when performing skin graft surgery [16]. Prophylaxis is an action or treatment to prevent disease, in this context, prophylaxis refers to antibiotics given before surgery. There are two main indications for the use of prophylactic antibiotics in skin graft surgery; first, to prevent infection of the surgical site, and secondly, to prevent infection of distal sites such as endocarditis [2]. Antibiotics can be administered via a plethora of different routes, typically they are given to the patient topically at the donor and surgical site or orally in the perioperative or postoperative[2] period [5]. Some dressings are even impregnated with antibiotics pre-emptively to allow for topical administration.

Aside from traumatic injuries such as de-gloving and burns, skin grafts are usually performed as an elective procedure. Subsequently, the majority of skin grafts take place on clean skin, leading to low rates of distal site infection and SSI following surgery [11,13]. This raises the question of the perceived benefits of prophylactic antibiotics in skin graft surgery as the infection rates are already low and there have been proven complications to the prolonged use of antibiotics [16]. Currently, we are in the midst of a growing antibiotic crisis with more and more new strains of drug resistant bacteria encountered in wounds with alarming frequency [7,4]. The continued use of prophylactic antibiotics may contribute to this which could lead to ineffective antibiotic therapy when treating an actively infected wound. Furthermore, antibiotics can have a range of systemic effects on the body ranging from nephrotoxicity [17] to anaphylaxis [9] in some, potentially putting patients at risk of death.

There are a number of alternatives to antibiotics which may be equally or more effective in preventing SSI. Iodine containing products, like betadine ointment, have proven antiseptic qualities in wounds and are associated with minimal complications [8]. Chlorhexidine, a disinfectant, has been shown to be even more effective than iodine in preventing SSI when used for decontamination of skin before surgery [3]. Honey and silver have also displayed success in preventing skin wound infection [12]. Indeed, silver impregnated dressings are widely used in plastic and dermatological surgery and present a viable alternative to antibiotics [6].

This ambivalence surrounding the use of prophylactic antibiotics in skin graft surgery is accompanied by a lack of guidance for surgeons. Although many surgeons do give prophylactic antibiotics [18], there is no significant literature to date assessing the benefit of antibiotic prophylaxis in relation to skin graft surgery. Therefore, given the numerous indications for skin grafts, the potential for misuse of antibiotics is high. This systematic review and meta-analysis seeks to analyze and summarize the current literature to assess the benefits and risks of antibiotic prophylaxis in skin graft surgery. Better understanding of the benefits and drawbacks of antibiotic prophylaxis for skin graft surgery can help provide clinical guidance as to the treatment of patients undergoing skin graft surgery. Here we present our protocol for our systematic review and meta-analysis.

[2] Strictly, post-operative antibiotic administration is subclinical treatment rather than prophylactic administration, often consisting of oral antibiotics for a period of up to 10 days (SHERRY L. MARAGH 2005).

2. Methods

This systematic review will be conducted in line with recommendations specified in the Cochrane Handbook for Intervention Reviews V.5.1.0 and is AMSTAR compliant [10] and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. This protocol has been developed a priori, and the systematic review has been registered a priori on the Research Registry® (www.researchregistry.com). UIN: reviewregistry656.

2.1. Criteria

The following inclusion and exclusion criteria will be used to minimize heterogeneity with previous reviews and address research questions.

2.1.1. Types of study included

All original research studies, levels 1–5 of the Oxford Centre for Evidence-Based Medicine (OCEBM Levels of Evidence Working Group n.d.) (randomized controlled trials (RCTs)) reporting original data on one or more of the outcomes of interest, will be considered for inclusion. Unpublished data and reports will also be considered if the methodology and data are accessible. Duplicate articles, cost-effectiveness studies, studies not reporting on primary data (review articles, editorials, discussions, commentaries, letters) will not be included. Studies not stating whether antibiotics were used and not reporting on the indication for skin graft surgery will be excluded.

2.1.2. Types of participants

The population of interest will be all adult patients undergoing elective skin grafts for delayed or immediate reconstruction, on any location of the body. Both full-thickness and partial/split thickness autografts will be included.

2.1.3. Types of intervention

The interventions of interest include all skin graft operations used for skin lesion removal. All studies reporting on outcomes following removal of all skin lesions (traumatic, congenital, malignant, benign), on any location in the body (head and neck, upper limb, lower limb, trunk), and reconstructing the skin using either full-thickness and split thickness skin grafts, on adult patients (>18 years) will be considered for inclusion. Studies reporting outcomes of cadaveric skin grafts will be excluded. Studies where skin graft is used post burns, or in for soft tissue coverage for example after amputation, ballistic or blast trauma, will be excluded. Studies will only be included if use of antibiotics is mentioned.

2.1.4. Types of comparators

Where comparative studies are included, outcomes will be compared between patients receiving and not receiving prophylactic antibiotics.

2.2. Outcomes of interest

The primary outcome will be incidence of a surgical site infection (SSI). Secondary outcomes, if reported, will include: length

of hospital stay (LOS), total wound healing time, revision surgery required, cost of medical care, and if stated, graft take and cosmetic appearance. These outcomes will be defined as follows:

1. Surgical site infection – An infection that occurs at the grafted (not donor) site of the surgical procedure, from any point after surgery until the skin graft has fully healed
2. Length of Hospital stay (LOS) – The length of time the patient resides in hospital after the procedure.
3. Total wound healing time – Time taken for surgical site to be completely healed
4. Revision surgery required – Any surgery performed on the same recipient surgical site due to a suboptimal outcome from primary surgery.
5. Cost of medical care – The monetary cost of the surgical procedure including any post-operative therapies.
6. Graft take – The level of incorporation of the graft with host tissue as measured by the paper of interest (e.g. as a percentage, or score on a visual analogue scale)

3. Search methods for identification of studies

Electronic databases will be searched, 1979–2018: PubMed, MEDLINE®, EMBASE, SCOPUS, CINAHL, PsychINFO, SciELO, The Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effect (DARE), the Cochrane Methodology Register, Health Technology Assessment Database, the NHS Economic Evaluation Databases and Cochrane Groups, ClinicalTrials.gov, Current Controlled Trials Database, the World Health Organization (WHO) International Clinical Trials Registry Platform, UpToDate.com, NHS Evidence and the York Centre for Reviews and Dissemination. Grey literature will be searched.

4. Search terms and keywords

The search strategy has been designed to identify articles focused on 'use of antibiotics for skin graft surgery'. A search will be conducted using appropriate keywords in English combined with Boolean logical operators as follows: ([antibiotics] OR [antibiotic]) AND ([skin graft] OR [graft survival] OR [surgical flap] OR [graft rejection] OR [skin) adapted to the appropriate syntax of each database. An example of the search strategy used on MEDLINE is shown in Table 1.

5. Identification and selection of studies

The articles identified from the electronic and manual searches will be recorded into a pre-formatted Microsoft Excel 2017 (Microsoft, Redmond, Washington, USA) spreadsheet. Duplicates excluded, along with the citation, titles and abstract.

Two researchers, acting independently, will screen articles for inclusion in two stages. First, titles and abstracts will be screened, and secondly, the full-text of articles selected in stage one will be retrieved and screened for inclusion. If necessary, authors may be contacted to clarify study eligibility, results, or to access an article. If there is uncertainty at stage 1, full texts will be retrieved. In cases of discrepancy, discussion over the inclusion of any particular study will take place between or arbitration by a senior author will take place to reach consensus. Articles that meet inclusion criteria at stage 2, will proceed to data extraction. Reasons for article exclusion at every stage will be recorded. Multiple reports of the same study will be linked together.

6. Data extraction, collection and management

Data extraction will be performed by two independently acting researchers with discrepancies over the inclusion of any particular

Table 1
Example search strategy using OVID

Database: Ovid MEDLINE(R) ALL <1946 to September 18, 2017>
Search Strategy:

1	antibiotic*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (333609)
2	exp Anti-Bacterial Agents/(661400)
3	skin graft*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (16845)
4	Skin Transplantation/(34524)
5	1 or 2 (811431)
6	3 or 4 (41819)
7	5 and 6 (1516)
8	perioperative.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (86422)
9	7 and 8 (28)
10	outcome*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2054474)
11	exp treatment outcome/(878748)
12	10 or 11 (2075484)
13	7 and 12 (356)
14	skin graft/(0)
15	exp skin graft/(0)
16	exp antibiotic agent/(0)
17	1 or 16 (333609)
18	1 or 16 (333609)
19	3 or 15 (16845)
20	18 and 19 (582)
21	exp treatment outcome/(878748)
22	20 and 21 (128)

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study resolved by consensus. Data will be input into a preformatted Microsoft Excel 2017 (Microsoft, Redmond, Washington, USA) database under standardised extraction fields under standardized extraction fields to facilitate easy and consistent data entry. Authors of any missing data will be contacted.

For each article the following data will be extracted:

- Article demographic details – Authors, Title, Year published, journal level of evidence, conflicts of interest, funding
- Patient demographic details – number of patients in total/in each group, mean follow-up (weeks), loss to follow-up (%), relevant comorbidities (vascular compromise, diabetes or other immunocompromising conditions)
- Indication for skin graft surgery - traumatic, congenital, malignant (SSC, BSC, melanoma), benign
- Surgical site – head and neck, upper limb, lower limb, trunk
- Type of skin graft – split-thickness, full-thickness
- Use of prophylactic antibiotics – 'yes' or 'no', route (per oral [PO], intravenous [IV], topical [TOP]), regimen (preoperative, intraoperative, perioperative, postoperative), duration (in days), class of antibiotics used (Fluoroquinoloes, penicillins, macrolides etc.)
- Surgical site infection – 'yes' or 'no', treatment (conservative, medical, surgical)
- Length of Hospital stay (LOS) - (days)
- Total wound healing time – (days)
- Revision surgery required – 'yes' or 'no'
- Cost of medical care - (dollars)
- Graft take – as measured by each study (e.g. % of incorporation/-failure, 'yes' or 'no')

7. Data analysis

Characteristics of included studies will be presented as counts and percentages. Continuous data will be expressed as weighted means differences (WMDs) with 95% confidence intervals (CIs). Categorical variables will be expressed as odds ratios (ORs) with 95% Confidence intervals. A meta-analysis using a random effects model will be conducted on Review Manager® version 5.1.7 (The Cochrane Collaboration, Oxford, UK) to assess compare the odds of rates of SSI with and without use of prophylactic antibiotic. If the heterogeneity is high a meta-analysis will not be conducted. For all statistical comparisons, significance will be set to $p < 0.05$.

7.1. Subgroup analysis

Additional analyses will be conducted to separately compare the rates of the secondary outcomes (LOS, cost of medical care, need for revision surgery) of interest between patients receiving and not receiving antibiotics. We also plan to compare the rate of SSI with lesion site and mean age of patient.

7.2. Heterogeneity

Inter-study heterogeneity will be explored for each variable using the Chi square statistic. I_2 values will be calculated to quantify the degree of heterogeneity across trials that could not be attributed to chance alone. Significant heterogeneity will be considered present when $I_2 > 50\%$. Two strategies will be used to assess data validity and heterogeneity; 1) funnel plots to evaluate publication bias and, 2) a subgroup analysis of higher quality studies (studies with quality scores > 10).

7.3. Quality scoring

The Grading of Recommendation Assessment, Development and Evaluation (GRADE) system (20) will be used to assess the overall strength of evidence of included studies. The GRADE system offers four levels of evidence: high; moderate; low; very low. RCTs are considered highest level of evidence. For RCTs the following will be assessed: 1) whether or not clinically relevant outcomes are reported; 2) whether results are comparable with protocols and subsequent publications where available. Key missing information across all study types such as follow-up times will be documented and assessed.

7.4. Assessment of bias

Risk of bias will be assessed using the Cochrane risk of bias tool (21). All included articles will be subjectively reviewed and assigned a value of "yes," "no," or "unclear" to the following questions: (i) Was the allocation sequence adequately generated? (ii) Was allocation adequately concealed? (iii) Was there blinding of participants, personnel, and outcome assessors? (iv) Were incomplete outcome data sufficiently assessed? and (v) Are reports in the study free of the suggestion of selective outcome reporting? Risk of bias plots will be generated.

8. Dissemination

This systematic review will provide a comprehensive analysis of the prophylactic use of antibiotics in skin graft surgery. Results have the potential to influence the care of patients receiving skin graft surgery for removal of skin lesions. The manuscript will be published in English in a peer-reviewed journal and the findings will be presented at national and international conferences.

Ethical approval

Not required for a protocol.

Funding

None.

Author contribution

MRB and AM conceived of the idea, MRB, VS, & MLL drafted the manuscript, KE, MC, RA and AM reviewed the final manuscript.

Conflict of interest statement

None.

Guarantor

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.isjp.2019.02.001.

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