

Infection and haemorrhagic complications associated with skin cancer surgery

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A thesis by publication for the award of PhD at Bond University, Gold Coast, Australia.

Declaration of originality

I certify, as the author of this thesis, and as first author of the publications arising, that I was the person primarily involved in the study designs, implementation, analysis and manuscript preparation. I declare that the work presented in the thesis is to the best of my knowledge and belief, original (except as acknowledged in the text) and that the work has not been previously submitted for a degree or diploma at any institution.

Anthony J. Dixon



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I would like to thank the many people who have contributed substantially to the process of developing this program of studies on complications and outcomes from skin cancer surgery. These include my supervisors during the period of studies:

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Mary P. Dixon B Appl Sci (Nursing) Skincanceronly

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I was originally enrolled in PhD studies at the University of Queensland but transferred mid studies to Bond University. For this reason, the principal supervisor altered from Professor Wilkinson to Professor Del Mar. Doctor Deborah Askew and Professor John Dixon were advising and supervising these studies in both the University of Queensland and Bond University periods.

Summary of research reported

Over four years from 2002 to 2006, a series of concomitant studies were undertaken to explore the complications and outcomes of skin cancer surgery. Specifically:

1. Through prospective studies, to identify risk factors for bleeding and infectious complications following skin surgery.
2. To determine through a randomized controlled trial whether mupirocin ointment versus paraffin ointment versus no ointment on a wound following skin closure affords the patient benefit.
3. To determine whether patients are at increased post operative bleeding risk should they remain on warfarin and / or aspirin prior to skin surgery.
4. To develop and then trial a novel approach (reducing opposed multilobed [ROM] flap) for below knee wound closures that may reduce the incidence of skin surgery complications on the leg and foot.
5. To investigate whether patients who suffer surgical complications are less likely to be satisfied with the service provision.

Methods

A prospective database was maintained for every patient attending the referral based Skincanceronly centre from July 1st 2002. Details of past history and skin cancer risk factors were obtained. Medications such as aspirin and warfarin were recorded. Procedures were documented including outcomes and complications of procedures. The type and site of all procedures was noted. Over the first 18 months of the data collection, patients were offered enrolment in a randomized controlled trial of placing ointment on wounds prior to a dressing being applied. These patients were also surveyed 6 months following surgery regarding their perceptions of the outcomes of such surgery. A new technique for closing defects below the knee was developed. After the technique had been used for 20 months, we retrospectively reviewed data and outcomes of this technique compared with traditional approaches.

Results

Skin surgery below the knee was found to be at increased risk of wound infection. Surgery on or near the ear was found to be at greater risk of post operative bleeding than other body sites. Warfarin therapy was found to be a risk factor for postoperative bleeding but aspirin did not alter bleeding incidence. Skin flap surgery and skin graft surgery resulted in both an increase in bleeding and infection incidence when compared to wounds closed directly. Placing mupirocin or paraffin ointment on a wound following suturing did not alter wound outcomes.

The reducing opposed multilobed (ROM) flap is a novel approach to close medium sized defects (11 to 45 mm diameter) below the knee. My data demonstrated a reduced flap necrosis incidence when compared to traditional closures. Overall complication incidence was also significantly reduced with this new technique.

Patients view of their scar outcome was a key indicator to their view of the overall skin cancer service provided. Patients rated wounds on the trunk poorly compared with wounds elsewhere on the body, including the face. Suffering complications did not alter patient perceptions of their skin cancer service.

Discussion

Postoperative bleeding following skin surgery was uncommon and was usually able to be managed conservatively. Adapting to patient perceptions of their skin surgery requires more than responding to complaints. An explanation and information regarding trunk scars may assist patients understanding that wound outcomes can be less aesthetic in these regions.

Antibiotic wound infection prophylaxis could be considered for: all procedures below the knee, wedge excisions of lip and ear, all skin grafts, and lesions in the groin. In view of the risk of antibiotic resistance, mupirocin ointment is not indicated for clean surgical wounds.

There was no case for discontinuing aspirin before skin surgery, but the INR should be monitored in patients taking warfarin. Skin surgery on or near the ear faces increased bleeding risk.

Clinicians could consider the ROM flap for elective defects below the knee from 11 to 45 mm in diameter. Satisfaction with the scar had the greatest influence on a patient's perceptions of their skin cancer service.

Limitations

A single experienced clinician in a southern Australia locale might not reflect complications, outcomes and perceptions of other clinicians in different cultures, climates and circumstances.

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Abstract

Background:

Skin cancer surgery remains the commonest elective procedure undertaken by medical practitioners in Australia. The most important complication of skin cancer surgery is recurrence and this is extensively reported on.

However, there is little published about other complications including (a) infection, (b) bleeding and (c) poor wound outcomes though complications are said to be at greatest risk below the knee. Nor is there much information about patients' perceptions of their skin surgery complications.

Aim:

This program of studies focused on three key areas of complications of skin cancer surgery; (a) infection, (b) bleeding and (c) surgery below the knee. Research methods included clinical trials with historical controls, observational studies and a randomized controlled trial

Setting:

A single doctor private medical practice confined to managing skin cancers on referral from their general practitioners.

Studies undertaken:

1) Wound infection

I first explored risk factors for wound infection following skin surgery. Through a three year prospective study I examined predictors of wound infection associated with managing 5091 skin lesions on 2424 patients. The overall incidence of wound infection was 1.5% (75/5091). Skin flap and skin graft surgery resulted in higher incidences of infection of 3% (47/1601) and 9% (6/69) respectively. Surgery below the knee proved the only body region of increased infection risk, at 7% (31/448). Post operative infection on the face was at low risk of 0.8% (18/2209).

2) Antibiotic ointment trial

To investigate whether this infection incidence could be reduced by application of ointment to the closed wound prior to dressing, I undertook a randomized controlled trial of mupirocin ointment (562 wounds on 262 patients) versus paraffin (729 on 269) versus no ointment (510 on 247). Neither ointment made a significant difference to any parameter tested, including infection incidence.

3) ROM Flap description

A novel skin flap repair (reducing opposed multilobed or ROM flap) was developed to attempt to address the increased incidence of wound infection below the knee. The flap was developed from first principles to minimise tissue tension and maximise tissue perfusion at the skin wound edge.

4) ROM Flap trial

The ROM flap was then subjected to a retrospective trial on 225 defects below the knee between 11 and 44 mm in diameter. The incidence of infection was not significantly lower in patients who had their defect repaired with the ROM flap at 9% (13/140) versus closure by traditional techniques at 13% (11/85) $p=0.36$. However, overall complication incidence at 14% (20/140) and end flap necrosis incidence at 1.4% were lower than in patients managed with this novel repair compared with traditional closures (32% and 7% respectively).

5) Warfarin and Aspirin

In a prospective trial involving 5950 skin lesions on 2394 patients over four years I maintained patients on their warfarin and aspirin medication prior to skin surgery unless the international normalized ratio was greater than 3.0. The overall bleeding incidence was 0.7% (40/5950). The following were independent risk factors for bleeding: age 67 years or older, odds ratio (OR) 4.7 (95% confidence interval, 1.8 to 12.2); $P=0.002$, warfarin therapy (OR 2.9, (1.4 to 6.3); $P=0.006$), and closure with a skin flap or graft (OR 2.7 (1.4 – 5.3); $P=0.004$). Aspirin therapy was not an independent risk factor for bleeding.

6) Bleeding locations

Next I investigated from this same data set of 5950 procedures whether certain body locations were at increased risk of postoperative bleeding. Only surgery in and around the ear demonstrated a significantly increased bleeding incidence at 2%, (OR 2.6 (1.2 to 5.7); $P=0.012$).

7) Perceptions

The final study addressed the patient's perceptions of their skin surgery through a prospective observational study. 778 consecutive patients were surveyed and 576 responded. Suffering infection, bleeding or other complications made no difference to the patient's perception of their skin cancer service. Scars on the trunk were more likely at 27% (21/77) to be rated neutral or negatively by the patient compared to non trunk scars at 7% (33/476) or on the face at 5% (15/305), $p<0.001$.

Limitations:

A single experienced clinician in a temperate southern Australia locale might not reflect complications, outcomes and perceptions of other clinicians in different cultures, climates and circumstances.

Conclusions:

Wound infection is at increased risk below the knee. Neither mupirocin nor paraffin ointment alter this risk or any other outcome assessed. The ROM flap reduces the incidence of overall complications for surgery below the knee but does not reduce the infection incidence.

There is no case for discontinuing aspirin before skin surgery but the INR should be monitored in patients taking warfarin. Skin surgery on or near the ear is predictive of bleeding. Suffering complications does not adversely impact on the patient's perception of their skin cancer surgery service.

Publications making up this thesis.

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Research into clinical practice publications

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24. Dixon A. The Multicenter Lymphadenectomy Trial Spells a Halt to Sentinel Node Biopsy. **CML Dermatology** 2006;11:1-5.
25. Dixon AJ, Dixon BF. Ultraviolet radiation from welding and possible risk of skin and ocular malignancy. **Med J Aust** 2004;181:155-7.

Background to this program of research

a) Overview:

There is remarkably little known about skin surgery complications and their risk factors. I was driven to explore further the causes of skin surgery complications so as my patients and patients in general may benefit. By understanding more about complications we may be able to help minimise them in the future.

I am in private clinical practice in Geelong, Australia. Here I manage solely patients with skin cancers or suspected skin cancers referred from other health care professionals, - largely general practitioners. The setting provides for an opportunity to launch a program of clinical studies to address some unanswered questions regarding skin surgery complications. I manage a large numbers of patients with a very narrow range of presenting complaints and diagnoses. Variation in surgical experience and technique would not act as a confounder within this program as I was the only clinician managing the patients. I had the opportunity to closely supervise all staff involved in the research program face to face. This minimized scope for straying outside of methodology and protocols. The setting was ready made for a substantial program to investigate complications and outcomes following skin cancer surgery.

Medicare data indicate excision of skin lesions including skin cancers is the most common surgical procedure undertaken in Australia.¹ It was apparent that if further knowledge could be gained regarding skin surgery complications then there was a potential benefit for many Australians. These procedures are undertaken by a wide range of medical practitioners including plastic surgeons, dermatologists and general surgeons. General practitioners manage the majority of skin lesions and skin cancers in Australia.¹ The most common and least serious of these skin cancers are basal cell carcinomas (BCCs), followed by squamous cell carcinomas (SCCs) and the more serious malignant melanoma.^{2, 3} Other uncommon skin cancers are also managed from time to time.⁴⁻⁸

Skin cancer can be managed with numerous surgical and non surgical approaches. These include wide local excision⁹⁻¹¹, frozen section micrographic controlled surgery (Mohs)¹²⁻¹⁵, urgent paraffin micrographic margin controlled surgery^{16, 17}, topical imiquimod¹⁸⁻²³, topical 5 fluorouracil^{24, 25}, photodynamic therapy^{26, 27}, cryotherapy²⁸⁻³¹ and curettage with or without ablation.^{30, 32-35} My practice incorporated all of the above modalities with the exception of Mohs surgery and photodynamic therapy. These two are the least used modalities in clinical practice in Australia. As such, assessing complications from my surgery could reflect most skin cancer procedures in this country.

Surgical wounds are being closed directly³⁶, by random pattern skin flaps³⁷, axial skin flaps³⁸, myocutaneous skin flaps³⁹, full thickness or partial thickness skin grafts.^{40, 41} This range of closures has been effected in my practice. Defects from 2 to > 200 mm in diameter were managed.

Measured outcomes from skin lesion excision include recurrence rates.^{28, 33, 42-49} Few studies have focused on other (non recurrence) complications of skin cancer management.

Frequent yet poorly addressed questions that may affect outcomes included:

- When should antibiotics be prescribed?
- Should warfarin or aspirin be ceased for skin surgery?
- Are young females the people most likely to be unhappy with skin surgery scars?
- Does antibiotic ointment on a wound reduce the infection risk?
- Are there parts of the body that suffer more complications than others?
- Are there reconstruction techniques that result in fewer complications than others?

No definitive answers to these questions were available from the literature. The incidence of complications in skin surgery is reportedly in around 6% of procedures.^{50, 51} Major life threatening complications are reportedly very rare.⁵²

Bleeding complications have been described as the commonest complication of skin excision surgery, accounting for about half of all complications, (3%).⁵¹ Infection incidence has been reported in the order of 2% of surgical excisions⁵¹ but can be as high as 8.6% in Australia.⁵³

The program of studies comprising this thesis was designed to answer these questions regarding complications of skin surgery especially bleeding and infectious complications. The core of this thesis is seven published original manuscripts.

I established a long term large prospective database powered to provide a suitable evidence base to examine risk factors for infection and bleeding complications following skin cancer surgery.

I also effected a randomized controlled trial of ointment on wounds to evaluate this common practice in dermatologic surgery.

Through a prospective trial I addressed whether or not remaining on warfarin and / or aspirin prior to skin surgery results in an increased post operative bleeding incidence.

Prior to establishing these clinical studies, my practice managed around 1,500 skin lesions per year, with just over half of these being malignant. I had managed around 5,000 skin cancers prior to establishing these clinical trials.

From the outset a long time course for these studies was envisaged. It would take many years to recruit sufficient patients to meet the power requirements of some of the planned studies. As such, I was aware that design, ethics approval, recruitment, analysis and publication would take up to seven years to complete regarding some of the studies.

The thesis also contains many educational pieces published with the aim of improving skin cancer knowledge for medical practitioners. The core published works are presented in this thesis in two columns and a different text colour and font to distinguish them from the single column non published text of this thesis.

My practice has been trading as “Skin Cancer Only”. Patients were and are not accepted for treatment without a referral from a health care professional, usually the patient’s general practitioner. It is a small private practice in Belmont, a suburb of Geelong, - the largest provincial city in Victoria. Coming from a rural background, I have a Fellowship of the Australian College of Rural and Remote Medicine (ACRRM). This College was only recognized for full specialist status in early 2007. I successfully completed the rural surgical program auspiced jointly by the Royal Australasian College of Surgeons and the Australian College of Rural and Remote Medicine in 1995.

b) Types of complications:

Complications associated with skin surgery can be local or distant to the treatment site.

Distant complications include metastatic disease⁵⁴⁻⁵⁶, anaesthetic anaphylaxis⁵⁷ and death.⁵⁸ Anaphylaxis can follow administration of local⁵⁷ and general anaesthetic agents.⁵⁹ A significant adrenaline dosage in the local anaesthetic can result in raised pulse and pressure along with patient anxiety.⁶⁰ Large doses of lignocaine in the local anaesthetic can result in cardiac dysrhythmias.⁶¹

Local complications can be classified as infective, bleeding, pain related⁶², wound complications, allergy⁶³⁻⁶⁵, recurrence^{47-49, 66-69} and others.

Infections in skin surgery wounds range from purulent suture foci through local cellulitis and infective necrosis to regional lymphadenitis and septicemia^{70, 71}. Unusually, infection might effect organs deep to skin such as osteomyelitis.⁷²

Bleeding complications include blood collection deep to the closed wound⁷³, (haematoma) and blood loss from the surface (haemorrhage).⁵¹ Bleeding complications can be further classified as intraoperative, postoperative and delayed.⁷⁴ Blood loss is able to be estimated allowing for further classifications based on volume of loss.⁷⁵

Pain complications following skin surgery include severe and persistent pain.⁷⁶

Wound complications occur in both the wound healing phase⁷⁷ and long term complications.⁷⁸

Wound healing complications include suture reaction^{79, 80}, flap necrosis⁸¹, dehiscence⁸², granuloma formation⁸³, persistent swelling⁸⁴, and ulceration⁸⁵, - all of which may be associated with delayed healing.⁸⁶

Long term poor wound outcomes include suture markings⁸⁷, keloid⁸⁸, hypertrophy⁸⁹, wound depression⁹⁰, elevation⁹¹, spread⁷⁹, hypo-pigmentation⁹², discolouration⁹², subcutaneous fibrosis⁹³, contour distortion and contracture⁹², - all of which may result in a suboptimal aesthetic outcome.

Allergic complications include allergy to skin preparations⁹⁴, latex or wound dressings^{95, 96}, pruritis⁹⁷ and contact dermatitis^{98, 99}. Common symptoms of contact dermatitis are; itch rather than pain, skin vesicles adjacent to wound, weeping. Causes include dressings, skin preparations, topical applications applied and latex.⁹⁹

Recurrence (non distant) can be classified as local⁶⁹, locally invasive into adjacent structures⁴⁶ and in-transit.^{48, 100, 101}

Other complications include an array of uncommon outcomes that are often related to the specific surgical site. This includes ectropion formation¹⁰² following surgery to the lower eyelid or cheek. Nerves may be damaged in skin surgery including the facial nerve¹⁰³, branches of the trigeminal nerve¹⁰⁴, the accessory nerve¹⁰⁵ and digital nerves.¹⁰⁶ Psychological consequences can also follow skin surgery.¹⁰⁷

While all of these complications have been described in the literature, there is, in the main, limited data on the incidence of each following skin surgery and less data on the risk factors for such complications.

c) Methods

The series of trials had a common and overlapping methodology prior to commencement.

The studies involved referred patients who attended the Skincanceronly clinic between July 1st 2002 and February 28th 2006.

Inclusion criteria were: patient aged 18 years or more, eligibility to give informed consent and ability to comply with treatment requirements; and the presence of a skin lesion for which procedural intervention was required.

- No patient was prescribed antibiotics prior to a procedure or following a procedure unless evidence of wound infection was apparent.
- No patient had his / her aspirin or warfarin ceased prior to or following surgery unless the International normalized Ratio (INR) was over 3.0
- Smokers were not asked to cease smoking prior to or following surgery.
- Details of past medical history were recorded including: diabetes, heart surgery, pacemaker, asthma, rheumatic fever, skin cancers, melanoma, and actinic keratoses.
- Medications being taken by patients were noted with specific questioning regarding warfarin, aspirin, immunosuppressants, and corticosteroids.
- Patients were asked if they smoked and if so how many per day.
- Patients were questioned regarding their hat wearing behavior and shirt wearing behavior.
- Patients were asked whether they had ever been sun burnt to the point of blistering.
- Patients were also asked whether they had worked in outdoor occupations and if so for how long.
- Patients were also asked regarding their sunscreen usage.
- Allergies to dressings and medications were also noted.

Data on patients including all the above information was recorded on a Microsoft Access database specifically designed from scratch on Microsoft Access by Dr. Anthony Dixon for the purposes of collecting and processing data for these series of studies.

One clinician (A.J.D) performed all procedures. Surgical techniques included punch biopsy, elliptical excision, incisional biopsy, full and partial thickness skin grafts, curettage and random pattern skin flaps. There were occasional axial or myocutaneous flaps undertaken as well as small number of partial thickness skin grafts. The site of all removed lesions was recorded and all specimens sent for histopathological examination. Where multiple tumours required excision, the most concerning lesion was excised first.^{108, 109}

Some consideration was given to the standard method of skin closure that would be implemented throughout this series of prospective studies. Despite some skin surgeons routinely closing all skin defects in two layers and others routinely closing in one layer, there has never been a randomized controlled trial to compare outcomes of these two popular approaches. The best evidence available comes from randomized trials of one versus two layer closure in obstetrics¹¹⁰, gynaecology¹¹¹ and vascular surgery⁸². The studies show very little if any difference. The largest of these studies and the study that most closely reflects skin lesion surgery is that by el Gamel⁸². In this well executed study, bilateral saphenous veins were harvested from 100 patients. Because intervention and control wounds were on the same patients, gender, age and other confounders were largely eliminated. There was no difference in wound complication rate.

Without a clear evidence base to determine whether wounds be routinely closed in one layer or two, an intermediate approach was implemented during these prospective studies. Most wounds were closed with a single layer of interrupted polyamide or nylon. Absorbable deep sutures were used in closure only if layers deep to the subcutis required direct closure. The absorbable sutures were either braided polyglycolic acid suture or monofilament poliglecaprone. Wounds selected for closure with two layers were larger wounds, those under greater tension and many on the trunk.

All patients were given a detailed postoperative instruction sheet regarding wound management, warning signs and details of return appointments. Patients were followed clinically until wound healing was completed, at least until removal of sutures and longer following skin flap or graft surgery, or if a complication developed.

The primary outcome measure of the studies was incidence of infection and postoperative bleeding. Other complications were also recorded.

Infection was recorded and classified as: purulent suture site, suture abscess, cellulitis, infective necrosis, large subcuticular abscess, regional lymphadenitis and septicaemia. When there was abscess formation or evidence of involvement beyond the local site, a wound swab was taken for culture; otherwise, the infection was assessed clinically. In the absence of suppuration, a wound was

considered infected if three out of the following signs were present: discharge, pain, erythema or induration. All wound infections were treated with oral dicloxacillin, 500mg orally four times daily, unless sensitivity or allergy deemed this to be inappropriate.

Any post operative haemorrhage or haematoma was recorded. A haematoma was regarded as small (up to 5 ml), medium (5 to 50 ml) or large (over 50 ml). A haemorrhage was regarded as small (up to 25 ml), medium (25 to 100 ml), or large (over 100ml).

Haemorrhage was further classified as delayed (1 to 24 hours after surgery) and late (more than 24 hours).

Other complications were recorded for each wound managed. Adverse scar outcomes were classified as: wound spread, suture markings, suture reaction, hypertrophy, keloid, discoloration, hypo pigmentation, wound depression, wound elevation, dog ears, and contracture.

Other local adverse outcomes recorded were post operative bleeding, allergy to dressing, allergy to skin preparation, contact dermatitis, local recurrence, subcutaneous fibrosis, granuloma, dehiscence, pruritus, persistent pain, nerve damage, ectropion, nodal involvement and distant metastases.

Post operative pain was also recorded as: no pain, minimal discomfort not requiring analgesia, mild pain relieved with paracetamol, moderate pain requiring stronger analgesia, severe pain unrelieved by analgesia, worst pain ever experienced.

Questionnaire at 6-month follow-up

A questionnaire was sent to all patients managed in the first 18 months of the trials. This questionnaire was an integral part of the patient perceptions and ointment randomized controlled trial. The questionnaire was first designed following a focus group asking patients what outcomes from their skin surgery they felt should be addressed in a formal study of outcomes from the consumer perspective. The questionnaire was considerably altered by the ethics review process including the addition of the "added comments" section at the end of the form.

Six months after surgery each patient was posted a one-page survey to complete and return (Figure 1). Any patient not returning the survey was sent another at 8 - 9 months after operation. The survey asked patients to rate the pain experienced and any inconvenience of the dressing, to comment on

their experience, to assess the final aesthetic appearance of the first operated area as excellent, very good, good, fair, poor or very poor, and to rate the quality of the service.

A sub analysis of the first lesions excised was performed for patients who had multiple lesions during the study period. Patients who had undergone multiple procedures were asked to rate only the first procedure.

The core peer reviewed published research will be presented in this thesis in a different type and colour of font and in two columns and on shaded paper to distinguish this material from the remainder of this work which will appear in full page width on white paper with black type.

Figure 1 Survey of participants 6 to 9 months following lesion excision.

How would you rate the wound discomfort from the time of the surgery?

- No pain
- Minimal discomfort that did not require pain killers
- Mild pain, relieved by Panadol, Panamax or Herron Paracetamol
- Moderate pain that required stronger pain killers to gain relief
- Bad pain that could not be relieved with pain killers
- The worst pain I have ever experienced

How would you rate the inconvenience of the dressing from the time of the surgery?

- No inconvenience
- A nuisance, but did not interfere with things
- Very disruptive or embarrassing to me
- Could not tolerate the dressing

Rate our performance as either:

Excellent, Very Good, Good, Fair, Poor or Very Poor to the following 12 questions:

How would you rate the time taken from being referred to Skincanceronly Clinic until the time you were assessed by our Doctor?

How well was the procedure explained to you in advance?

How would you rate the time taken to have your skin surgery?

How effective was the local anaesthetic?

How would you rate the actual operation?

How would you rate the nursing / reception staff?

How well was the pathology result explained to you?

How good was the follow up care by Skincanceronly Clinic?

How good was the final look of the scar?

How would you rate the cost of your treatment at Skincanceronly Clinic?

How good was any written material provided?

Overall, how do you rate our service?

Please feel free to add any comments

d) Statistical analysis

Demographic details were presented as percentage or mean \pm standard deviation (SD) as appropriate. Chi-square method (Fisher exact) was used to test the significance of differences between proportions and categorical variables.

Analysis of the ointment random controlled trial (RCT) was conducted on an intention to treat basis. Patient characteristics and differences between groups in each trial were assessed with analysis of variance using Tukey post-hoc analysis, Kuskall-Wallis H test and chi-square test as appropriate.

Key outcome incidences were analyzed using the chi-square test. The antibiotic ointment (RCT) was compared with controls individually using 2 x 2 tables.

In addition this method was also used to assess univariate risk of bleeding / infection estimates and these were presented as odds ratios with 95% confidence intervals (bleeding).

Multivariate analysis (bleeding) was tested using binary logistic regression (forward and backward) and odds ratio beta-coefficients with 95% confidence intervals shown.

Receiver operator characteristic curves to assess an age cut off value that represented the best combination of sensitivity and specificity for risk of a bleeding complication.

The SPSS 12.0.01 and later 14.0.2 (Chicago, Illinois,) statistical software was used for all statistical analysis. A p-value of less than 0.05 was considered statistically significant in all studies.