Protocol

ECHO study

The Effect of Copper on the Healing of Obstetric wounds

VERSION 3 – 17/09/2015

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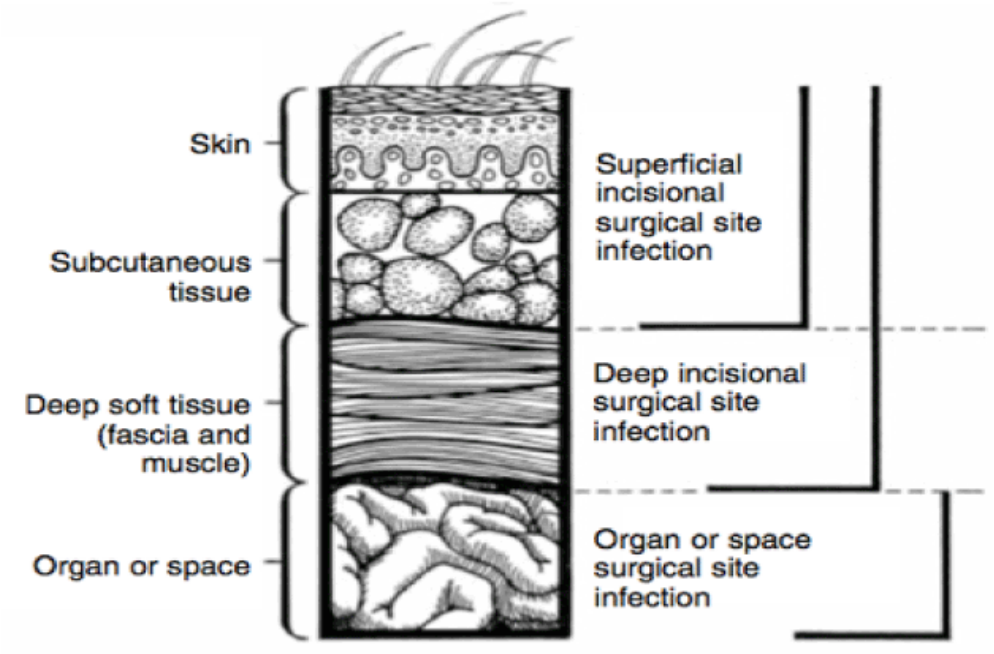
Full title: Randomised controlled trial on the effect of copper impregnated dressings and maternity pads on the healing of obstetric wounds and wound infection

Background

In Croydon Health Services around 4,000 babies are born annually and the vast majority are born vaginally. The most common complication of vaginal delivery is perineal or vaginal laceration with a prevalence as high as 85% and up to 70% will need suturing (1). Within Croydon Health Services 73% deliver vaginally of whom 66% sustain perineal laceration (19% first degree, 74% second degree, 7% 3rd/4th degree) and an episiotomy is performed in 24% of the vaginal deliveries. Minor lacerations are often left unsutured, whereas the majority of the second or higher degree tears will be sutured directly after delivery. Due to supporting factors such as a moist environment and the presence of high numbers of bacteria, perineal trauma is associated with wound infection and affects 11% of the women with sutured tears (2). Wound infection can cause pain, dehiscence, delayed wound healing and interfere with a woman's ability to nurture their baby and enjoy motherhood (3).

The caesarean section rate worldwide is rising (4) and the rate in Croydon University Hospital is in the region of 25% of all deliveries. The most significant source of maternal morbidity after caesarean section is postoperative infection (surgical site infection) and can be the cause of a prolonged hospital stay, readmissions (5) sepsis and maternal death (6). Surgical site infection is one of the most prevalent reported nosocomial infection, which accounts for 14-16% of all hospital-acquired infections. Despite prophylactic antibiotics, the rate of wound infection after caesarean section is ranging between 7% and 41% (7-9). According to the Centers for Disease Control and Prevention (CDC), surgical site infection can be classified as an incisional infection, either superficial or deep, or an organ or space infection, such as endometritis (10). See figure one for the CDC surgical site classification.

Figure 1 CDC Classification for Surgical Site Infections



The micro-organisms that are most commonly the cause of the infection of perineal tears and caesarean section wounds are Enterococci, Streptococci, Staphylococci, Gram-negative bacteria and anaerobes (5, 11). As a consequence of antibiotic resistance, MRSA infection is becoming an increasing challenge. Several studies have detected MRSA colonisation rates of up to 10% in rectovaginal swabs in asymptomatic pregnant women (12, 13). MRSA has been proven to cause more severe postpartum infections, especially after caesarean section (14-16). Although several strategies to eliminate or reduce colonisation of MRSA such as skin wash have been studied, the real efficacy of such interventions remains inconclusive (17). Moreover, the preoperative skin preparation using chlorhexidine, which reduced the overall rate of surgical site infection, was found ineffective among MRSA carriers (18).

Antimicrobial copper

The antimicrobial effect of copper has been known for centuries. As early as 2600-2200 BC the Egyptians used green copper rust for the treatment of chest wounds and to sterilise drinking water. In another Papyrus it was written that copper splinters, shavings and various

copper salts and oxides were used to treat headaches, burn wounds, itching and skin infections (19). With the increase in antibiotic resistant bacteria causing nosocomial infections, copper has become a popular subject of recent research. There are many laboratory studies showing the biocidal effect of copper on a wide range of microbes such as bacteria, fungi and viruses (20, 21). Copper has also been proven to be effective against Methicillin-resistant Staphylococcus aureus (MRSA) (22) and Vancomycin-resistant Enterococci (VRE) (23). The use of copper surfaces within the hospital setting has been evaluated in several clinical studies showing significant reductions in bacterial colonisation on copper surfaces compared to standard materials (24). After the use of copper as a biocidal contact surface, the use of copper impregnated textiles was explored. Although there is a variety of containing copper impregnated textiles available such as socks, pyjamas, underwear, bed linen, face masks, stockings and wound dressings, there is a paucity of clinical research. There has however been a clinical study on the effect of copper impregnated socks in patients suffering from tinea pedis and this revealed a significant improvement or resolution of the infection after wearing these socks for two weeks (25).

Wound healing

Copper is assumed to be involved in several processes crucial for wound healing (26). A key role in wound healing is angiogenesis. It has been shown that copper induces the production of vascular endothelial growth factor (VEGF) and therefore stimulates angiogenesis (27). Furthermore, copper promotes wound healing due to an elevation in integrin expression (28); enhancement of fibrinogen stabilisation (29) and up regulation of several enzymes essential for matrix remodelling and cell growth (30). Several laboratory studies have demonstrated an association between a copper dependant enzyme, lysyl oxidase (LOX), and skin ageing and pathological skin conditions (31).

Safety

The dermal exposure to copper is considered safe as copper is not only an essential element for normal skin function but also essential for the immune system and blood coagulation (32). In contrast to microorganisms, human skin cells have the ability to metabolise and utilise copper (33) and therefore the development of adverse reactions are unlikely.

Our hypothesis is that copper impregnated fibres in maternity pads and surgical wound dressings, reduces infection rates in perineal lacerations, episiotomies and caesarean section wounds.

Aim

The aim of this study is to investigate the impact of copper impregnated wound dressings and maternity pads on the incidence of infection in perineal wounds after vaginal delivery and caesarean section wounds.

Objectives

Primary:

1. To assess the effect of copper impregnated wound dressings on the incidence of wound infection following caesarean section.
2. To assess the effect of copper impregnated maternity pads on the incidence of wound infection of second degree perineal tears following vaginal delivery.

Secondary:

1. To assess the effect of copper impregnated wound dressings on other maternal outcomes, such as length of hospitalisation, readmission rate and pain of the wound.
2. To assess the effect of copper impregnated maternity pads on other maternal outcomes, such as length of hospitalisation, readmission rate and perineal pain.

Methodology

This is a double blind randomised controlled pilot study to assess feasibility of copper impregnated wound dressings and maternity pads for the healing of obstetric wounds. All pregnant women in Croydon University Hospital who attend their routine second-trimester scan appointment at approximately 20 weeks of gestation will receive a detailed patient information sheet (Appendix 1 Patient Information Sheet) about the four arms of this study. When women are eligible to participate after delivery, informed consent will be obtained (see Appendix 2 Informed Consent).

All women who are planned to have an elective caesarean section will be recruited at their antenatal clinic appointment. A detailed patient information sheet specific for the caesarean section arm of this study will be given prior to consent. Informed consent will be obtained antenatally. After caesarean section, confirmation of willingness to participate in this study will be obtained and documented directly after elective caesarean.

All patients will be assessed by telephone at baseline, 7, 14, and 30 days. The recruitment period will be 12 months.

The inclusion criteria are:

- Aged 18 or over
- Delivered by caesarean section (emergency or elective),
  or vaginally, sustaining a perineal tear or episiotomy which needed to be sutured
- Ability to understand the content of the patient information sheet (in English, via an interpreter if needed and possible)
- Ability to give informed consent

The exclusion criteria are:

- Inability to give consent
- Fetal or neonatal death or poor neonatal outcome
- Obstetric anal sphincter injuries
- Included in another study on postpartum infection conducted in the Obstetrics and Gynaecology Department
- Wilson's disease
- Allergy to copper

Randomisation

After inclusion all patients will be randomised for a wound dressing or maternity pad with (study group) or without copper (control group). The two sets of wound dressings and pads will be marked "A" or "B". Both the clinician and the patient will be blinded to the randomised group. Only the manufacturer will be aware of which group contains copper.

Copper impregnated dressings

As soon as possible, but within 12 hours after primary closure of the caesarean section incision, the randomised study dressing will be applied. The two study dressings will be equivalent to the dressing normally used within this Trust, except that one set of dressings will have a thin top layer of non-woven polyester fibres with 3% copper oxide ions permanently attached to it. According to local protocol the wound dressing will be left intact for 7 days following surgery and will be renewed if necessary.

Copper impregnated maternity pads

As soon as possible, but within 12 hours after suturing women will be asked to wear the study maternity pads, which will be provided. The two sets of study maternity pads will be equivalent to the currently recommended pads, except that one set of pads will have a thin

top layer of non-woven polyester fibres with 3% copper oxide ions permanently attached to it. Women will be asked to use the pads for 14 days after delivery.

Patient data, history and physical examination:

Demographic data such as age, ethnicity, height and weight will be collected as well as obstetric data and delivery details (Appendix 4 Datasheet). Past medical history such as concomitant (chronic) diseases and the use of medications will be obtained. Wound infection will be assessed via a telephone questionnaire after 7, 14 and 30 days after delivery.

The data will be stored in a secure room within Trust facilities. All electronic data will be stored within password protected IT system within the Trust, which is only accessible by the clinical and research team.

Questionnaire

For the assessment of surgical site infection, the Post Discharge Questionnaire (see Appendix 5 Post Discharge Questionnaire) used by the HPC surgical site infection surveillance will be used, which is according to the worldwide used definition of surgical site infection by the CDC (10). Since the Post Discharge Questionnaire is dependent on the women's report rather than confirmation following clinical assessment of the wound, the criteria for infection have modified to allow for easy interpretation of the reported symptoms as follows:

- Criterion 1: discharge pus AND antibiotics prescribed
- Criterion 2: clinical signs* AND dehiscence
- Criterion 3: Clinical signs* AND antibiotics prescribed

  *clinical signs: at least 2 of the following must be present: pain, heat, redness or swelling

Without clinical assessment of the wound, the type of SSI cannot be defined.

Since there is no commonly used definition in the literature for wound infection following perineal tears, the Post discharge Questionnaire with the modified criteria for infection will be used for the perineal tears as well.

Microbiological assessment

When wound infection is suspected according to the above explained criteria, a wound swab is taken to detect the causative organisms.

Statistical analysis

Statistical analysis will be performed using SPSS version 20.0 or higher. Infection rates in the perineal tear group and the caesarean section group will be analysed. The infection rates in the study group (with copper) will be compared to the control group and possible risk factors for infection will be explored.

Sample size calculation

Since the effect of copper on infection rates is currently unknown, we will conduct a pilot study for 12 months. After 3 months we will perform an interim analysis to be able to calculate the sample size.

Maternity statistics at Croydon University Hospital	
	Past 12 months (N=3752)
Vaginal deliveries (N=2734)	
Episiotomy	643
2nd degree tear	1334
Total sutured tears (excl 3rd/4th degree tears)	1977
Caesarean Section (N=1018)	
EmCS	696
ElCS	322
Total study population	**2995**

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