A review of the literature examining the relationship between temperature and infection in surgical wound healing

Tweed C

Abstract

Wound infection following surgery is a relatively common and serious complication. Perioperative hypothermia increases risk of surgical wound infection by several mechanisms including cutaneous vasoconstriction and a decrease in the activity of the immune system. This paper reviews these mechanisms and concludes that both prevention of hypothermia and application of local and systemic heat may assist in reducing the incidence of surgical wound infection.

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Introduction

Normal wound healing is a complex interaction of biochemical and physiological mechanisms that initiate, regulate and discontinue this biological event [1]. Wound infection inhibits these multiple processes with a disturbed host-bacteria equilibrium in favour of the bacteria [2].

Wound infection following surgery is a common, debilitating and expensive outcome for many patients [3]. The Public Health Laboratory Service in the UK estimate that for each patient with a surgical infection, there is an additional hospital stay of 6.5 days and a doubling of hospital costs [3].

Temperature

Although core temperature is normally anywhere between 36.7^{0}C and 37^{0}C [4], skin temperature varies depending upon the environment and is controlled by the sympathetic nervous system allowing thermoregulation [4]. Thermoregulation, however, is profoundly impaired by the effects of anaesthesia [5-8] and, unless actively warmed, the majority of patients will become hypothermic. Major surgery typically causes a fall in core temperature of 1-3^{0}C [9], with as many as 60% of patients affected [10]. Since the beginning of recorded history of medicine, humans have used hot packs to treat their wounds; however, with the use of antibiotics, it appears that locally applied heat has fallen into relative disuse [11].

The surgical wound is affected by temperature primarily via its relationship with perfusion and the host immune response [12]. Tissues that are inflamed and infected require increased amounts of oxygen; one way that this can be achieved is to increase the perfusion and an effective way of achieving this is by the application of heat [11].

Infection

In a controlled clinical and microbiological sampling trial using 65 patients, Raahave *et al.* [13] determined that the risk of acquiring a surgical wound infection was based on both susceptibility of the surgical wound to contamination and quantitative bacterial levels.

Miles *et al.* [14] defined a 'decisive period' where infecting microorganisms either persist and develop into an established infection or are suppressed by local host immunity. This paper deserves in depth review as it is widely referred to in studies where surgical wound infection and hypothermia have been researched [15-18].

Carol Tweed
BSc (Hons) RGN
Masters Candidate
Wound Healing Research Unit
University of Wales College of Medicine
Cardiff, UK
Part-time Consultant
Huntleigh Healthcare UK and New Zealand
E-mail: caroltweed@hotmail.com

Miles *et al.*[14] used a guinea pig model and injected nine different bacteria into the skin. Dependent upon bacteria, between 50 and 99.99% of the infecting dose were rendered ineffective by host defence mechanisms in a healthy animal within the first 2 hours of inoculation. When there was reduction of perfusion by local injection of adrenaline or by general systemic dehydration 2 hours prior to bacterial injection, the effect of the infection was greatly enhanced. However, when this was repeated 5 hours after initial inoculation, there was little or no effect. Similar effects were noted when the work was repeated looking at the action of antibiotics. In addition to the importance of the timing of these events, this study demonstrates in guinea pigs that host defences are dependent upon blood perfusion.

Despite these results being of great potential clinical significance and cited in several subsequent clinical studies, this work has not been replicated and the effect may not necessarily be evident in human subjects. There are also a number of other criticisms of the work including the fact that only one of the bacteria used was a natural pathogen in guinea pigs and it is unclear how standardisation took place, how any bias was eradicated or whether there was any analysis of variance.

Another study confirming the importance of this so called 'decisive' time period was conducted by Classon *et al.*[19] using a population of 2847 patients. There was demonstration of how the period immediately prior to and during surgery itself was optimal for effective antibiotic administration, with administration after the surgical incision being less effective. This effect is thought to be due to the fact that antibiotics present in blood at the time of injury become trapped in the fibrin clot where they exert their effect[12].

Surgical wound infection and hypothermia

It has been proposed that perioperative hypothermia increases predisposition to wound infection by several mechanisms:

- Cutaneous vasoconstriction[20-22] results in a decrease in subcutaneous perfusion and oxygenation[12, 23, 24] and reduced amounts of collagen deposition, thus decreasing the tensile strength of the wound[17, 25].
- A decrease in the activity of the immune system:
  - via neutrophil oxidative killing[9, 26, 27].
  - by suppression of the inflammatory response by altering T-cell cytokine production[28, 29].

Animal studies

Sheffield *et al.*[15, 16] conducted two very similar controlled randomised studies using anaesthetised guinea pigs. In the first of these[15], the core body temperatures of 32 animals were maintained at either 39^{0}C (normothermic for guinea pigs), 36^{0}C or 41^{0}C. One hour after anaesthesia, 2x10^8 *Escherichia coli* were injected into eight sites on the animals' backs.

Results were determined by measurement after 24 hours of the indurated area of bacterial injection using a standard model for evaluating resistance to infection[14]. There were significantly ($p<0.05$) larger areas of induration on the hypothermic animals compared to the normothermic or hyperthermic groups. The animals, however, were not at the designated core temperature until 1 hour post injection of bacteria and this may have had implications, as the results of work by Miles *et al.*[14] had shown that it was likely that there was a 2 hour 'decisive' period when infections were most likely to become established. Despite achieving statistical significance, the authors state that "the magnitude of the effect was not large" which indicates that results may not be clinically important, particularly when extrapolated to a human population.

In a very similar study later the same year, Sheffield *et al.*[16] investigated the effects of hypothermia and resistance to *Staphylococcus aureus* dermal infection in a group of 24 guinea pigs. As in the previous work, only a small effect was noted, despite achieving statistical significance. The need to undertake human outcome studies was highlighted by the authors.

Human studies

Kurz *et al.*[17] conducted a double blind randomised study in a group of 200 patients undergoing colorectal surgery to test the hypothesis that perioperative normothermia would reduce the incidence of surgical wound infection. Core temperatures of the experimental group were maintained at a mean of 36.6^{0}C by use of forced air warming blankets and warmed intravenous fluids. The temperature of the control group of patients was allowed to decrease naturally to a mean value of 34.7^{0}C.

Although pre-operative risk of infection scores between the two groups were similar, there were six surgical wound infections in the normothermia group compared to 18 in the hypothermic group, demonstrating a statistical significant difference of 0.009. There were also significant differences with respect to white blood cell counts between the two groups, with leucocytosis being impaired in the hypothermic group on the first post-operative day and being higher 2 days later.

A subgroup of 30 patients in the normothermia group and 24 patients in the hypothermia group were also evaluated for amounts of collagen deposition in the healing wound at 7 days post-operatively. Results demonstrated that there was

significantly more collagen deposited near the wound in normothermic patients as compared with the hypothermic group.

In discussion of the results, the authors consider that the likely mechanism for the increase of infection in the hypothermic group was the timing of the hypothermic episode and refer to the previous work of both Miles *et al.* [14] and Classon [19].

A criticism of the Kurz [17] study is that, prior to commencing the main data collection, a pilot study was performed which calculated that a sample size of 400 patients would be required in order to provide a 90% chance of identifying a difference. Despite this, the study was stopped after 200 patients as incidence of wound infection was statistically different between the two groups ($p<0.01$). However, as highlighted by Abrams [30], the decision to stop any clinical trial early is controversial, complex and should not solely rely on statistical calculations. Allowing the trial to continue may have possibly resulted in different outcomes, despite the interim analysis at 200 patients.

Conflicting results to the Kurz [17] study were obtained by both Munn *et al.* [31] and Barone *et al.* [32]. In a small retrospective case controlled study using patient charts and records, Munn *et al.* [31] compared two groups of 18 women from a cohort of 900 women undergoing caesarean section. It was concluded that hypothermia was not a risk factor in post-operative wound infection in this subject group. A major difference between this and other studies is that the subjects were healthy and that pregnancy results in increased vascularity, something that was acknowledged by the authors. Additionally, mean core temperatures exceeded 36^{0}C in both groups and thus neither group could be considered to be hypothermic. There were also inconsistencies in both measurement and timing of temperature. In addition, average temperatures were compared between subjects both with and without wound infection. In view of these criticisms, it is difficult to compare the results of this study with that of others.

Barone *et al.* [32] criticised the work of Kurz *et al.* [17] regarding aspects of the methodology, specifically with respect to the fact that hypothermic patients were given both prophylactic antibiotics and blood transfusions. In a retrospective study of 150 consecutive patients having colonic surgery, Barone *et al.* [32] concluded that hypothermia did not result in an increase in post-operative wound infections. However, the study design of Barone *et al.* [32] could be criticised as being limited since a retrospective technique of reviewing patient charts was used and not all the issues to do with Kurz's [17] study were specifically addressed.

Flores-Maldonado *et al.* [33] undertook a non-randomised prospective study using a group of 290 consecutive patients to examine the association between mild perioperative hypothermia and surgical wound infection. Despite stating that a similar methodology to that of Kurz *et al.* [17] was used, it is clear from reviewing the methodology that this was not the case. The surgery type was different and took a mean of 54 minutes compared to a mean of 3 hours in the Kurz study. Despite these differences, however, the study came to the same conclusion as that of Kurz in that hypothermia was found to be an independent and significant risk factor for surgical wound infection with a relative risk of 6.3 ($p=0.01$).

Most recently, Melling *et al.* [18] published results of a randomised controlled study of 421 patients to assess whether infection rates in short duration clean surgery with a mean time of 48 minutes could be reduced by warming patients. This study consisted of three arms, namely the control group, who received normal treatment, and then two experimental groups, who each received either local warming via the application of a non contact radiant heat dressing or systemic warming by use of a forced air warming blanket. There was a statistically higher rate of wound infection in the non-warmed group compared to the combined warmed groups ($p=0.001$) and there was also statistical significance when the two warmed groups were considered individually. The authors again cite the study by Miles *et al.* [14] and suggest that the effect may be due to not only the decisive period during and after surgery but that preventing vasoconstriction in the hour before surgical incision may be of equal importance.

Mechanisms by which hypothermia affects surgical wound healing

Perfusion

Perioperative hypothermia causes peripheral vasoconstriction which, in turn, reduces perfusion [22], reduces collagen deposition and tensile strength [17, 25], reduces oxidative killing [34] and increases the risk of surgical wound infection [12].

In a prospective study of 130 general surgical patients, reduced subcutaneous wound oxygenation and risk of infection have been demonstrated to be statistically associated [24]. Additionally, subcutaneous oxygen tension has been shown not only to be a powerful predictor of wound infection [24, 35], but also the single most important factor affecting neutrophil respiratory burst [27].

The immune response

In a review of immunomodulation, McBride *et al.* [36] summarise how anaesthetic drugs may impair immune response in patients undergoing surgery. Despite this, the

immune response is considered to be a major host defence against surgical contamination [2]. Although there are many mechanisms by which this may take place, including phagocytosis, diapepedesis and opsonisation [37], it is likely that oxidative bacterial killing by polymorphonuclear leucocytes (PMN) is the most important host defence [27, 34, 38]. The oxidative system within the PMN converts atmospheric oxygen to free radicals which then oxidise bacterial cell walls [34]. This process is dependent upon the perfusion of oxygenated blood in the tissues and, if this process fails, the contaminating bacteria, inflammatory cells and the tissue itself all compete for oxygen and bacterial killing is depressed [34].

In two separate studies, van Oss *et al.* [38] and Johansen *et al.* [26] studied the effect of temperature on human PMN function *in vitro*, specifically investigating chemotaxis, phagocytic engulfment, digestion and oxygen consumption. Both studies demonstrated that PMN activity increased up to and including a temperature of 40^0C, after which function deteriorated. The implications of these *in vitro* studies are that the febrile response to infection may enable optimal PMN activity; there is some evidence to suggest that moderate pyrexia can be therapeutic in the management of some general systemic infections [39, 40].

In a group of 10 patients undergoing colorectal resection, Wenisch *et al.* [9] demonstrated, using both *in vivo* and *in vitro* techniques, the effect of mild perioperative hypothermia on phagocytotic and reactive oxygen intermediates activity in the PMNs. The results obtained were consistent both in the *in vitro* and *in vivo* groups, as well as with those of a previous study undertaken [38], demonstrating that there was a statistically significant impairment of neutrophil function by mild hypothermia lasting only as long as the hypothermic episode.

Within the methodology, no reasons are given for selection of this diagnostic group and no explanation of how sample size with sufficient power to detect clinically important treatment effects was established. Additionally, there is no reporting of randomisation method. A further criticism is that despite there being a control group, a warmed group and a reported 4^0C range, the results illustrate that there was less than 1^0 difference between some subjects in the warmed group and the non-warmed group.

In addition to the patient studies of Wenisch *et al.* [9], *in vitro* temperature manipulations were also evaluated which consisted of blood samples from matched control subjects. Although the link is made between cause and effect, the authors discuss that this could occur either directly or indirectly (via for example cytokines or stress hormones) and this was not possible to determine from using this methodology. They suggested that further work in patients using a more complex methodology is required to prove that hypothermia results in impaired neutrophil oxidative killing, although it seems likely that this is the case.

In a randomised controlled trial of 60 patients undergoing a variety of routine abdominal surgical operations, Beilin *et al.* [28] investigated the effects of mild perioperative hypothermia compared to normothermia in terms of cellular immune responses. Differences in some immune responses were observed between the two study groups, with the hypothermic group demonstrating significant ($p<0.05$) reductions in mitogenic lymphocytic stimulation, IL2 and IL-1ß.

Core temperatures of patients were measured by an oesophageal probe; however, blood samples were taken from unspecified peripheral veins and it is likely that the temperature will have been different between the two sites. Although differences were observed, there is no analysis of variance within this study despite the fact that within the discussion it is acknowledged that type of anaesthesia, duration of surgery, blood transfusion and neuroendocrine changes can all affect immune function [41]. Another factor that is not clear from the methodology is whether the blood analysis within the laboratory of the hypothermic patients was conducted at ambient room temperature or at the same temperatures as the patients core temperature. This is a potential flaw of undertaking such work and was highlighted by Johansen *et al.* [26].

It is apparent from the studies reviewed in this paper how there are differences in design, definitions of hypothermia, type and duration of surgery, site and method of temperature measurement and other confounding variables. This makes it difficult to generalise results, although the trends suggest that temperature has a significant effect on outcome.

Conclusion

Factors common in surgical environments include cold, pain, blood volume deficit and various medications, all of which induce the sympathetic nervous system, resulting in peripheral vasoconstriction [12].

A review of the literature in this paper suggests that preventing hypothermia during the operative procedure prevents vasoconstriction and enhances both local perfusion and immune function and as a result incidence of surgical wound infection is reduced. These actions appear to take place via an increase in wound oxygen tension [24].

It is unlikely that all surgical wound infections will ever be prevented; however, in the battle between host defence and

bacterial invasion, the chances of infection can be greatly minimised by maintaining the host defences at peak efficiency[2]. Both prevention of hypothermia and application of local and systemic heat may be able to facilitate this process.

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