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Effect of hypothermia on haemostasis and bleeding risk: a narrative review

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Abstract

It must be remembered that clinically important haemostasis occurs in vivo and not in a tube, and that variables such as the number of bleeding events and bleeding volume are more robust measures of bleeding risk than the results of analyses.

In this narrative review, we highlight trauma, surgery, and mild induced hypothermia as three clinically important situations in which the effects of hypothermia on haemostasis are important. In observational studies of trauma, hypothermia (body temperature $<35^{\circ}$C) has demonstrated an association with mortality and morbidity, perhaps owing to its effect on haemostatic functions. Randomised trials have shown that hypothermia causes increased bleeding during surgery. Although causality between hypothermia and bleeding risk has not been well established, there is a clear association between hypothermia and negative outcomes in connection with trauma, surgery, and accidental hypothermia; thus, it is crucial to rewarm patients in these clinical situations without delay. Mild induced hypothermia to $\geq 33^{\circ}$C for 24 hours does not seem to be associated with either decreased total haemostasis or increased bleeding risk.

Keywords

Hypothermia, coagulopathy, haemostasis, bleeding, trauma, surgery, injury

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Introduction

Many studies have been conducted to investigate the effects of hypothermia on haemostasis, and these have yielded contradictory results. These varying outcomes may be explained by differences in the methods used to study platelet function and

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coagulation. Furthermore, some of these studies have only investigated mild hypothermia whereas others have tested a broader spectrum of temperature ranges, including deep hypothermia.

Over the course of evolution, animals have developed different methods of maintaining an ideal body temperature. Cold-blooded animals, also known as ectothermic animals, cannot regulate their body temperature internally so their body temperature varies according to their environment. In contrast, warm-blooded, or endothermic, animals, including humans, maintain a constant body temperature via endogenous mechanisms. Such mechanisms include the internal generation of heat, which is mainly an incidental effect of the animal's routine metabolism. Under conditions of excessive cold or low activity, an endotherm may utilise special mechanisms adapted specifically for heat production. Examples include special-function muscular exertion, such as shivering, and uncoupled oxidative metabolism within brown adipose tissue.[1,2] It is thought that endothermic animals need to keep their body temperature constant to ensure enzyme activity and complex homeostasis, such as haemostasis.[3] In humans, hypothermia has been demonstrated to slow enzyme activity.[4,5]

It must be remembered that clinically important haemostasis occurs in vivo and not in a tube. All analyses of coagulation and platelet function have limitations and measure only part of the total haemostatic system. To evaluate bleeding risk or determine the cause of bleeding, clinicians must recognise which part of the total haemostatic system is being analysed and, perhaps more importantly, which part is not being analysed with the methods used. The usual testing systems have no natural flow, which means that the natural intersection of blood flow with the endothelium cannot be measured.[6] Furthermore, many coagulation tests are performed at 37°C, which means that any temperature-dependent coagulation disturbances may be overlooked.[7]

Previously, hypothermia was always treated because it affects many biological systems, e.g., coagulation and platelet function. In modern medicine, hypothermia is used as a treatment in some situations, such as after cardiac arrest, to protect the brain from further damage after ischaemia. Research has also been conducted on the potential of therapeutic hypothermia to protect organs other than the brain from ischaemic organ injury via protective mitochondrial effects.[8]

The aim of this review was to describe how hypothermia may affect bleeding risk, coagulation, and platelet function in trauma, surgery, and mild induced hypothermia, three clinically important situations in which the effects of hypothermia on haemostasis are important.

Materials and methods

We performed a PubMed/MEDLINE and Embase search using the search terms "hypothermia," "coagulopathy," "bleeding," and "bleeding risk," which were combined with "surgery," "trauma," "injury," and "induced hypothermia." Both authors carried out electronic searches and reviewed the bibliographies of retrieved articles to identify further studies of interest. The authors conducted additional searches, content revision, and discussion until agreement was reached.

Results

Figure 1 presents an overview of the study findings regarding the manner in which hypothermia affects outcomes and haemostasis under clinical conditions of trauma, surgery, and mild induced hypothermia.

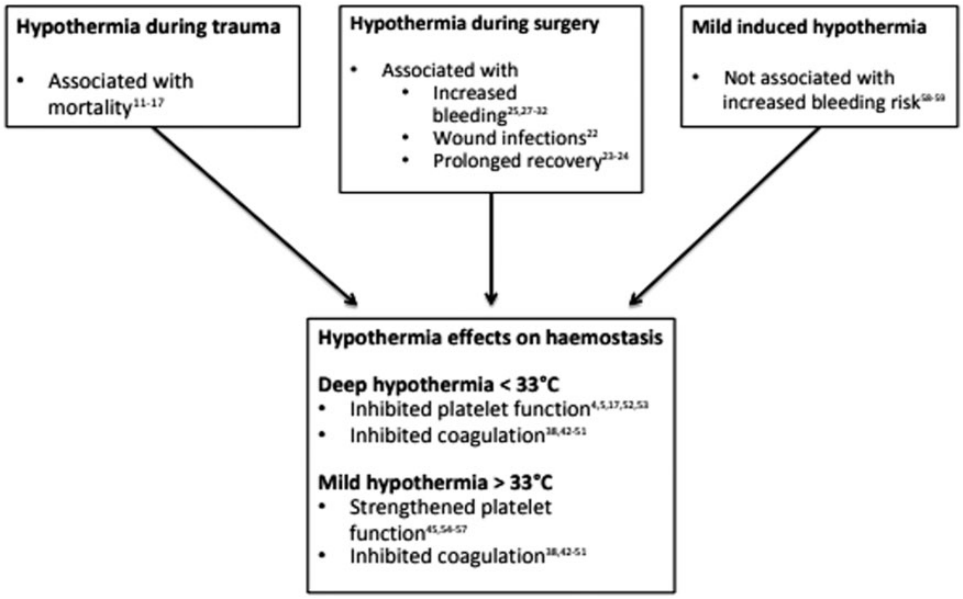

Figure 1. Summary of how hypothermia affects outcomes and haemostasis in three clinical conditions.

Trauma

Undesirable hypothermia, along with acidosis and coagulopathy, is part of the lethal triad that worsens the prognosis of patients with severe trauma.[9] Heat is lost at the scene of trauma in the emergency department when the clothing is removed and when room-temperature fluids are administered. Furthermore, patients who are in shock have disrupted body temperature regulation and lower tissue metabolism, which decrease the amount of heat that they produce. During surgery, heat loss is exacerbated by the exposure of the peritoneum. It has been estimated that a patient undergoing damage-control laparotomy loses as much as 4.6°C of core body heat per hour.[10]

An impressive number of observational studies have examined the effects of hypothermia after trauma. Unfortunately, but for obvious reasons, prospective randomised trials are largely unavailable. Many observational studies have demonstrated an association between trauma-induced hypothermia, defined as body temperature <35°C, and morbidity and mortality.[11–17]

The effects of undesired hypothermia in trauma are many;[18] hypothermia may alter myocardial contractions, induce arrhythmias, or cause trauma-associated coagulopathy. From an immunological perspective, hypothermia may diminish the inflammatory response and increase the risk of pneumonia.[19] Because hypothermia is more common in severely injured patients, it is difficult to determine whether it contributes to mortality independently of injury severity. Thus, even if there is a strong association between accidental hypothermia after trauma and mortality or morbidity, causality between hypothermia and bleeding risk has not been convincingly established. The increased risk of death and morbidity may be dependent on any of the negative effects of hypothermia or increased bleeding risk.

Surgery

General anaesthesia inhibits the thermoregulatory system[20] and may cause undesired hypothermia in unwarmed patients. Several studies have described how hypothermia causes complications such as morbid myocardial outcomes,[21] surgical wound infection,[22] prolonged recovery,[23] and hospitalisation.[24] Furthermore, patients who undergo long major operations are more likely to become hypothermic than those undergoing shorter minor procedures; these patients are also likely to lose more blood. Consequently, retrospective correlations between hypothermia and blood loss are especially likely to be confounded and should be interpreted carefully.

During surgery, it is crucial that the haemostatic system functions properly, to stop minor bleeding. In fact, surgery provides a useful potential research model for randomised interventional studies to determine whether mild hypothermia constitutes a risk factor for blood loss and/or transfusion requirements in comparison with normothermia. Several studies have provided evidence of the manner in which mild hypothermia affects the haemostatic system during surgery. In an initial study, hypothermia was found to increase both blood loss and transfusion requirements.[25] These findings were not confirmed in a later study, which reported that hypothermia did not increase either blood loss or transfusion requirements.[26] Since then, various studies have reported that mild hypothermia increases blood loss and/or transfusion requirements,[27–32] does neither,[21,33–35] and even reduces blood loss.[36]

In a meta-analysis including investigations of how hypothermia during surgery affects bleeding and transfusions, it was concluded that even mild hypothermia (<1°C) significantly increases blood loss by approximately 16% (4%–26%) and increases the relative risk of transfusion by approximately 22% (3%–37%).[37]

Mild induced hypothermia

Conventional wisdom holds that hypothermia reduces coagulation and platelet function and impairs primary and secondary haemostasis. Whether this is also true of mild induced hypothermia (≥33°C) has been debated.[38] Concerns have been raised regarding whether mild induced hypothermia can be applied safely after cardiac arrest because external chest compressions, dual anti-platelet inhibition after primary percutaneous coronary intervention, and the insertion of arterial and venous lines are frequent in such situations. Bleeding issues were among the reasons that the first clinical study[39] and the initial guidelines[40] on hypothermia after cardiac arrest excluded patients with bleeding diathesis.

Several studies have investigated how mild induced hypothermia affects coagulation and platelet function. Conventional coagulation tests (i.e., prothrombin time/international normalised ratio) suggest that activated partial thromboplastin time and platelet count seem unaffected by mild hypothermia when analysed under normothermia, but these show a progressively hypocoagulative response when analysed at the temperature of the patient.[41] Wohlberg et al.[5] performed similar experiments and only demonstrated a hypothermic effect at temperatures below 33°C. Using the Sonoclot instrument, Shimokawa et al.[42] demonstrated a significant hypocoagulative response upon analysing the patient's own hypothermic body temperature. Other visco-haemostatic assays, such as thromboelastography or rotational thromboelastometry, have also been used to investigate hypothermia applied both in vivo and in vitro. The overall results of these studies have shown delayed clot initiation and propagation if the analyses are

performed with instruments set to the temperature of the hypothermic patient but not if performed under normothermic conditions.[38,43–51]

Investigations of how platelet function, with or without platelet inhibitors, is affected by hypothermia have yielded divergent results. Some authors have described decreased platelet function in response to deep hypothermia.[4,5,17,52,53] We have previously shown markedly increased platelet activity, measured via flow cytometry, in response to mild hypothermia to $\geq$33°C applied in vitro in whole blood from patients with acute coronary syndrome who were treated with ticagrelor and aspirin.[45] This finding is in agreement with several other studies, in which in vitro incubation at mild hypothermia of whole blood taken from healthy volunteers resulted in increased platelet reactivity. Scharbert et al.[54,55] used multiple-electrode aggregation to demonstrate increased platelet aggregability in response to in vitro application of mild hypothermia ($\geq$33°C). Högberg et al.[56] found an increase in ADP-stimulated platelet aggregation after temporary clopidogrel treatment in hypothermic (33°C) blood compared with normothermic blood. Ferreiro et al.[57] used multiple-electrode aggregation testing to investigate the effect of in vitro application of hypothermia in blood from clopidogrel-treated patients; those authors concluded that mild therapeutic hypothermia is associated with impaired response to clopidogrel therapy. In conclusion, mild induced hypothermia to $\geq$33°C seems to increase platelet aggregation whereas deep hypothermia (<33°C) appears to decrease platelet aggregation.

It is likely that the increased time to clot initiation and impaired clot propagation demonstrated in visco-haemostatic tests under mild induced hypothermia may be counteracted by increased platelet aggregation and that this can be demonstrated with multiple-electrode aggregometry and flow cytometry. However, given that there is no perfect coagulation or platelet measurement capable of evaluating the risk of bleeding, it would be extremely interesting to investigate the number of bleeding events that occur during mild induced hypothermia, as a clinically relevant surrogate measure of bleeding risk. In fact, this was done in the Targeted Temperature Management (TTM) trial.[58] In that study, 950 comatose survivors of out-of-hospital cardiac arrest were randomised into body temperature conditions of either 33°C or 36°C for 24 hours. The TTM study was sufficiently powered to detect differences in mortality and neurological outcomes but also showed that there were no differences in serious bleeding complications between the groups. Furthermore, in a sub-study of the TTM trial, we recently demonstrated that there was no difference in the incidence of bleeding during the first 3 days of intensive care after cardiac arrest between the 33°C and 36°C groups.[59] This can be considered indicative of the safety of mild induced hypothermia to $\geq$33°C with regard to bleeding complications.

Discussion

In this narrative review, we highlight trauma, surgery and mild induced hypothermia as three clinically important situations in which the effects of hypothermia on haemostasis are important but remain under debate. In observational studies of trauma, undesirable hypothermia demonstrates a strong association with mortality and morbidity, perhaps owing to the effects of hypothermia on haemostatic function. Randomised trials have shown that undesirable hypothermia causes increased bleeding during surgery. In mild induced hypothermia, decreased coagulation ability has been shown to be counteracted by increased platelet aggregation. Moreover,

in a large randomised trial (the TTM study), no differences were observed in bleeding events between groups, indicating that mild induced hypothermia to $\geq$33°C is safe, from the standpoint of bleeding.

It should be noted that mild induced hypothermia to $\geq$33°C is applied in the hospital, together with careful optimisation of all other physiological and laboratory values. This is a completely different situation than that of hypothermia at the scene of trauma or during surgery, where hypothermia occurs in an uncontrolled manner and is often accompanied by hypervolemia and acidosis.

The increased platelet aggregation seen in mild induced hypothermia is well recognised in previous studies.[45,54–56,60,61] Furthermore, under normal conditions, blood flow is maximal at the centre of the vessel, and platelets are marginalised to the periphery and close to the scene of injury, thus promoting platelet–endothelial interaction.[62] Given that the viscosity of blood is increased in hypothermia, as previously shown,[63] this marginalisation effect is more prominent in a hypothermic situation, as is shear-induced platelet aggregation.[64] Higher blood viscosity during hypothermia decreases blood flow velocity, which also facilitates the formation of a platelet plug because the forces that tend to draw the platelet plug from the vessel wall are decreased. These are all pro-coagulative factors that are not easily measured in vitro but that are present during hypothermia in vivo.

The platelet count drops during hypothermia,.[51,65] but this decrease in platelet count is reversible when the normal body temperature is restored. This phenomenon is also observed in hibernating animals, whose platelet counts increase very quickly during arousal, indicating a storage-and-release phenomenon rather than decreased and increased production.[66]

When the body temperature drops below 37°C, platelets become more predisposed to activation by thrombotic stimuli, an occurrence known as priming. The ability to prime at peripheral body sites, where temperatures are lower and the chances of trauma higher, is thought to have evolved as a protective effect against bleeding, whereas more central body sites have greater protection against thrombosis.[67] It can also be speculated that, from an evolutionary perspective, it is appropriate that platelets are activated when they are exposed to lower temperatures, as is the case in open bleeding.

Increased platelet activity during mild to moderate hypothermia is counteracted by decreased coagulation ability, presumably caused by inferior enzyme activity in the coagulation cascade during hypothermia.[4,5] In an experiment performed in 1960, thromboplastin time was measured at a range of temperatures from 0°C to 40°C, in whole blood from both the cold-blooded South African clawed toad (*Xenopus laevis*) and from humans. The results showed that the thromboplastin time for blood from the toad was nearly constant at around 30 s between 10°C and 40°C and peaked at just over 1 minute at 0°C. In human blood, the thromboplastin time increased exponentially below 20°C and reached 13 minutes at 0°C.[68] This illustrates how the blood of cold-blooded animals adjusts to temperature changes and how the blood clotting system of warm-blooded animals is considerably more limited in terms of optimal temperature range.

Conclusion

Even though the causality between hypothermia and bleeding risk is not well established, there is a clear association between undesirable hypothermia (body temperature <35°C) and negative outcomes in connection with trauma, surgery, and

accidental hypothermia, and it is crucial to rewarm patients in these clinical situations without delay. Mild induced hypothermia to $\geq$33°C does not seem to be associated with either decreased total haemostasis or increased bleeding risk.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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