The Effects of Mild Perioperative Hypothermia on Blood Loss and Transfusion Requirement

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Background: Anesthetic-induced hypothermia is known to reduce platelet function and impair enzymes of the coagulation cascade. The objective of this meta-analysis and systematic review was to evaluate the hypothesis that mild perioperative hypothermia increases surgical blood loss and transfusion requirement.

Methods: The authors conducted a systematic search of published randomized trials that compared blood loss and/or transfusion requirements in normothermic and mildly hypothermic (34–36°C) surgical patients. Results are expressed as a ratio of the means or relative risks and 95% confidence intervals (CI); $P < 0.05$ was considered statistically significant.

Results: Fourteen studies were included in analysis of blood loss, and 10 in the transfusion analysis. The median (quartiles) temperature difference between the normothermic and hypothermic patients among studies was 0.85°C (0.60°C *versus* 1.1°C). The ratio of geometric means of total blood loss in the normothermic and hypothermic patients was 0.84 (0.74 *versus* 0.96), $P = 0.009$. Normothermia also reduced transfusion requirement, with an overall estimated relative risk of 0.78 (95% CI 0.63, 0.97), $P = 0.027$.

Conclusion: Even mild hypothermia (<1°C) significantly increases blood loss by approximately 16% (4–26%) and increases the relative risk for transfusion by approximately 22% (3–37%). Maintaining perioperative normothermia reduces blood loss and transfusion requirement by clinically important amounts.

ANESTHETIC-induced thermoregulatory impairment[1–3] produces hypothermia in unwarmed surgical patients. Hypothermia results initially from an internal core-to-peripheral redistribution of body heat[4,5] and subsequently from heat loss exceeding metabolic heat production.[6] Prospective randomized trials indicate that even mild hypothermia (approximatey 2°C) causes severe complications including morbid myocardial outcomes,[7,8] surgical wound infection,[9,10] prolonged recovery[11] and

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hospitalization,[9] negative nitrogen balance,[12] shivering,[13] and thermal discomfort.[14]

Hypothermia also impairs platelet function, primarily by impairing release of thromboxane A_2, which is necessary for formation of an initial platelet plug.[15,16] Hypothermia also impairs function of enzymes in the coagulation cascade. This effect is often unrecognized clinically because coagulation tests are normally performed at 37°C, irrespective of the patient's actual core temperature. When various *in vitro* tests are performed at various temperatures, however, impairment is obvious.[17–22]

Whether mild perioperative hypothermia causes a clinically important coagulopathy remains controversial. An initial study that specifically evaluated this question found that hypothermia increases both blood loss and transfusion requirement.[23] However, a subsequent similar study reported that hypothermia increased neither.[24] Since then, various studies have reported that mild hypothermia increases blood loss and/or transfusion requirement,[25–31] does neither,[7,32–34] or even reduces blood loss.[35] We thus present a systematic review and meta-analysis evaluating the hypothesis that mild perioperative hypothermia increases surgical blood loss and transfusion requirement.

Materials and Methods

We conducted a systematic search for published, randomized, controlled trials that compared normothermic patients with those who had mild intraoperative hypothermia (34–36°C). Among these studies, only trials that reported blood loss, transfusion requirement, or both as an outcome were included in the analysis. Studies in which average core temperature decreased to less than 34°C or in which local cooling was used to decrease bleeding from the surgical site were excluded. Trials with sample sizes smaller than 15 were also excluded. Two authors independently scrutinized each published report and selected those to be included in the analysis using the above criteria.

The medical literature published since 1966 was searched in all languages using electronic databases. The initial search included the MEDLINE (1966–2006), PubMed, and Cochrane library (2006) databases. The search commands used individually and in various combinations included "intraoperative," "perioperative," "normothermia," "hypothermia," "blood loss," "transfusion," and "complications." The bibliographies of the retrieved articles were reviewed for additional relevant studies. Our last electronic search was in October 2006.

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The information obtained from the studies included the number of patients, American Society of Anesthesiologists physical status if available, type of surgery and anesthetic used, operating room temperature, patient's core body temperature at the end of surgery (T_{Core}), amount of blood loss, number of patients receiving transfusion, and the transfusion requirements. The extracted data included the intraoperative blood loss and the total amount of blood loss if it was mentioned in the trial. When possible, authors were contacted to request missing information.

Traditional meta-analysis methods were used to assess the comparative effect of normothermia *versus* hypothermia on both total blood loss and whether a patient received any transfusion. We analyzed total blood loss under the assumption that loss follows a log-normal distribution, with the raw data being skewed to the right, as this is the usual experience with blood loss data. Blood loss was reported as mean $\pm$ SD in 9 of the 14 studies,[23–26,28,30,32–34] as median and range in 2 studies,[27,31] and as mean $\pm$ SE in 3 studies.[7,29,35] We converted these summary statistics to the mean (SD) of the log-transformed blood loss that would be expected under the log-normal distribution.[36] Specifically, the log-transformed mean and SD, say μ and σ, were estimated as

$$\mu = \log\left(\frac{(\mathrm{MeanX})^2}{\sqrt{(\mathrm{SDX})^2 + (\mathrm{MeanX})^2}}\right),$$

$$\sigma = \sqrt{\log\left[(\mathrm{SDX}/\mathrm{MeanX})^2 + 1\right]},$$

where MeanX and SDX are the mean and SD of the untransformed data, respectively. The effect of normothermic *versus* hypothermic temperature was then summarized as the ratio of normothermic to hypothermic mean blood loss for each study and overall, where a ratio of 1.0 indicates no association. Because of the log scale, the reported effect size is actually the ratio of geometric means. Our use of the ratio of means instead of the difference in means allows intuitive comparison of studies with quite differing volumes of blood loss.

We used a random effects (instead of fixed effects) meta-analysis method for each outcome because we were interested in generalizing beyond the included studies.[37] Heterogeneity of the treatment effects was assessed for each meta-analysis using the Q statistic and associated *P* value. Because of the relatively high proportion of zeros, or patients with no transfusion, the amount of transfused blood was not normally or even log-normally distributed in the studies considered. Therefore, instead of using the observed amount of transfused blood, we performed a meta-analysis on the relative risk of any transfusion *versus* no transfusion in the normothermic *versus* hypothermic patients. A relative risk less than 1.0 indicates that the estimated risk of

transfusion is less for those in the normothermic *versus* those in the hypothermic groups.

Publication bias was assessed using funnel plots, which are plots of the SE *versus* the observed treatment effects and their 95% confidence intervals (CIs). Standard error has been shown to be the best variable to plot against the treatment effect in funnel plots for most types of meta-analyses.[38] A vertical line indicates the summary treatment effect. Diagonal lines form a funnel that expands as SE increases (and thus as the sample size decreases) and indicates the expected 95% CI width (±1.96 SE) for each SE on the vertical axis. In the absence of heterogeneity, 95% of estimated treatment effects (not their CIs) are expected to fall within the funnel. Symmetry indicates lack of publication bias.

We calculated and reported quality scores and their individual items to give a rough description of the relative quality of the included studies. A formal incorporation of the quality scores into our meta-analysis was not performed because of the problems with quality scores in general, including bias and subjectivity.[39] We did, however, assess whether there was an obvious correlation between the estimated treatment effects and the quality scores. Our meta-analysis does account for the size of each study by inverse weighting on the variance, as is customary.

A quality score for each blood loss study was formed by adding points for the following factors: whether blood loss was a primary outcome (3 points if yes, 0 otherwise); whether an objective measure of blood loss was used (2 points if yes, 0 otherwise); whether method of randomization was specified (1 point if yes, 0 otherwise); and whether intent-to-treat analysis methodology was specified or implied (1 point if yes, 0 otherwise) for a possible range of 0 to 7 quality points.

As an additional analysis, because there was naturally some degree of variability in the within-study mean temperature difference among studies, we assessed the correlation between this difference (*e.g.*, mean temperature for normothermic and hypothermic groups) and the resulting blood loss treatment effect using Pearson correlation weighted for study size. R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. The significance level for each hypothesis was 0.05.

Results

Our initial search of the electronic databases using key words retrieved approximately 1,800 articles. Among these, we excluded from the analysis retrospective studies or those in which the core temperature reduced to less than 34°C, local cooling methods had been used, or the sample size was smaller than 15. We found a total of 18 studies that met our criteria. Fifteen trials reported

Table 1. Summary of Total Blood Loss Literature Review

Reference	Type of Surgery	Patients (n)		T_{core} (°C)		Blood Loss (ml)		Reported P Value
		NT	HT	NT	HT	NT	HT	
Schmied et al.[23]	Hip arthroplasty	30	30	36.6 ± 0.4	35.0 ± 0.5	1670 ± 320	2150 ± 550	<0.001
Winkler et al.[31]*	Hip arthroplasty	75	75	36.5 ± 0.5	36.0 ± 0.4	1531 (1055, 1746)	1678 (1366, 1965)	0.031
Widman et al.[30]	Hysterectomy	29	29	Δ0.4 ± 0.3	Δ0.9 ± 0.4	923 ± 410	1068 ± 482	0.048ᶜ
Persson et al.[29]†	Hysterectomy	29	30	36.8 ± 0.1	35.8 ± 0.1	186 ± 27	308 ± 47	<0.05
Hofer et al.[26]	Off pump CABG	22	24	36.8 ± 0.1	35.8 ± 0.1	1497 ± 497	2300 ± 788	<0.001
Bock et al.[25]	Major abdominal surgery	20	20	Δ0.5 ± 0.8	Δ1.5 ± 0.8	635 ± 507	1070 ± 802	<0.05
Johansson et al.[24]	Hip arthroplasty	25	25	36.5 ± 0.8	35.4 ± 0.9	1047 ± 413	1066 ± 441	0.88‡
Smith et al.[35]†	Major surgery	31	30	36.7 ± 0.1	36.1 ± 0.1	423 ± 101	159 ± 49	<0.05
Frank et al.[7]†	Major surgery	142	158	36.7 ± 0.1	35.4 ± 0.1	390 ± 70	520 ± 60	0.16
Mason et al.[28]	Gastric bypass	32	32	36.3	35.7	111 ± 40	157 ± 73	<0.01
Casati et al.[32]	Hip arthroplasty	25	25	36.3	35.7	470 ± 170	442 ± 216	>0.05
Murat et al.[33]	Spine surgery	26	25	36.5 ± 0.8	35.4 ± 0.9	160 ± 61	161 ± 100	>0.05
Hohn et al.[27]*	Cardiac	43	43	36.0 ± 0.4	35.3 ± 0.4	660 (230, 1870)	956 (340, 5480)	<0.05
Nathan[34]	Cardiac	73	71	36.7 ± 0.4	34.3 ± 0.4	596 ± 356	666 ± 405	0.28

Data reported as mean ± SD except as noted.

* Data reported as median (min, max).   † Data reported as mean ± SEM.   ‡ P value calculated from summary data.

CABG = coronary artery bypass graft; HT = hypothermic; NT = normothermic.

blood loss, of which seven reported only intraoperative loss,[7,25,28,29,32,33,35] two reported only postoperative loss,[27,34] and five reported both intraoperative and total loss.[23,24,26,30,31] One study was excluded from the analysis because of inconsistent reporting of results.[40] Thirteen studies compared transfusion requirements in normothermic *versus* hypothermic patients. Three trials were excluded[7,8,41] because there was no mention of the number of patients requiring transfusion. Hence, 14 studies were included in analysis of blood loss whereas 10 studies were included in the transfusion analysis.[9,23–27,30,31,34,35]

Pertinent summary statistics are given in tables 1 and 2 for studies included in the meta-analysis of total blood loss and transfusion, respectively. The respective blood loss and transfusion studies evaluated a total of 1,219 and 985 patients. The median (quartiles) of the mean temperatures reported for patients in the normothermic

groups among the 14 blood loss studies was approximately 36.6°C (36.4°C, 36.7°C), whereas it was 35.6°C (35.4°C, 35.8°C) in patients assigned to hypothermia. The median (quartiles) temperature difference between the normothermic and hypothermic studies was only 0.85°C (0.60°C, 1.1°C). A summary of the quality scores for the studies that were included in the total blood loss meta-analysis is given in table 3. Quality scores and the items used to create them were not included in the meta-analysis and are reported as a means of summarizing and comparing the rigor of the various included studies. Quality score was not correlated with the observed effect size (Pearson correlation [95% CI] 0.30 [−0.27, 0.72], P = 0.30). Meta-analysis results are given in figures 1 and 2, with summary statistics for each study and the overall result, and including a forest plot depicting the effect of interest. Effect sizes for total blood loss

Table 2. Summary of Transfusion Literature Review

Reference	Patients (n)		Any Transfusion (%)		T_{core} (°C)		Transfusion (ml)		Reported P Value
	NT	HT	NT	HT	NT	HT	NT	HT	
Schmied et al.[23]	30	30	1	7	36.6 ± 0.4	35.0 ± 0.5	10 ± 55	80 ± 154	0.02
Winkler et al.[31]*	75	75	29	40	36.5 ± 0.5	36.0 ± 0.4	289 ± 408	401 ± 470	0.058
Widman et al.[30]	29	29	9	11	Δ0.4 ± 0.3	Δ0.9 ± 0.4	190 ± 220	290 ± 330	>0.05
Hofer et al.[26]	22	24	5	11	36.5 ± 0.4	35.6 ± 0.8	155 ± 285	530 ± 689	0.048
Bock et al.[25]	20	20	3	9	Δ0.5 ± 0.8	Δ1.5 ± 0.8	95 ± 293	502 ± 754	<0.05
Johansson et al.[24]	25	25	15	13	36.9 ± 0.6	36.0 ± 0.7	490 ± 490	525 ± 595	>0.05
Smith et al.[35]*	31	30	2	1	36.7 ± 0.1	36.1 ± 0.1	525 ± 175	700‡	>0.05
Hohn et al.[27]†	43	43	17	18	36.0 ± 0.4	35.3 ± 0.4	548 (190, 1500)	566 (100, 2050)	>0.05
Nathan et al.[34]	73	71	23	24	36.7 ± 0.4	34.3 ± 0.4	245 ± 490	245 ± 420	0.76
Kurz et al.[9]	104	96	23	34	36.6 ± 0.5	34.7 ± 0.6	140 ± 350	280 ± 420	<0.01

Data are reported as mean ± SD unless noted otherwise.

* Data reported as mean ± SEM.   † Data reported as median (min, max).   ‡ Only one patient.

HT = hypothermic; NT = normothermic.

Table 3. Quality Scores for Blood Loss Studies

Reference	Method of Randomization	Intent to Treat	Blood Loss Primary Outcome	Objective Measure of Blood Loss	Quality Score*
Schmied et al.[23]	1	1	3	2	7
Winkler et al.[31]	1	1	3	2	7
Widman et al.[30]	1		3	2	6
Persson et al.[29]	1	1			2
Hofer et al.[26]	1			2	3
Bock et al.[25]		1			1
Johansson et al.[24]	1	1	3	2	7
Smith et al.[35]					0
Frank et al.[7]	1	1			2
Mason et al.[28]	1	1			2
Casati et al.[32]	1	1			2
Murat et al.[33]		1		2	3
Hohn et al.[27]				2	2
Nathan et al.[34]	1	1		2	4

* Correlation between observed effect size and the quality score nonsignificant ($P = 0.30$).

were found to be heterogeneous across studies ($Q = 62.3$, $P < 0.001$), indicating significant variability among the studies, whereas transfusion effect sizes were more homogeneous ($Q = 11.4$, $P = 0.25$). The estimated ratio of geometric means of total blood loss (95% CI) in the normothermic *versus* hypothermic groups was 0.84 (0.74, 0.96), $P = 0.009$. Our results thus indicate that normothermia is associated with significantly lower blood loss than hypothermia, at least for the aggregate types of surgeries considered and for normothermia and hypothermia as defined in these studies. Normothermia as defined in these studies is also associated with a reduced need for transfusion compared with hypothermia, with overall estimated relative risk of 0.78 (95% CI 0.63, 0.97), $P = 0.027$.

The funnel plots in figures 3 and 4 do not indicate substantial publication bias for either total blood loss or transfusion, although potential bias is difficult to evaluate with the moderate number of studies in this meta-
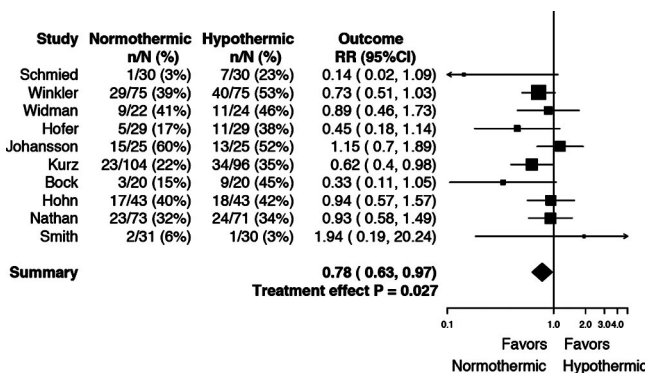

Fig. 2. Transfusion meta-analysis and forest plot. Treatment effect is expressed as the relative risk (RR) of transfusion in normothermic *versus* hypothermic patients. Normothermia is associated with 22% less risk of transfusion than hypothermia (95% CI 3%, 37%), $P = 0.027$. n = number transfused; N = number of patients.

analysis. However, some publication bias for smaller studies is seen by the imbalance in the lower half of each figure. Studies with estimated effects outside the funnel are evidence of heterogeneity for blood loss (fig. 3), as noted above, whereas the transfusion effects are more homogeneous (fig. 4).

Among the three coronary artery bypass graft studies included in the meta-analysis, two[26,34] did not use cooling methods to induce hypothermia during cardiopulmonary bypass. As per randomization, patients were either warmed to normothermia or allowed to develop mild hypothermia. Only in the study by Hohn et al.[27] were the patients actively cooled to 28°C before randomization at the end of cardiopulmonary bypass. The results of the meta-analysis are similar when this study was excluded; the summary ratio of means (95% CI) for total blood loss is 0.85 (0.74, 0.97), and summary relative risk (95% CI) for transfusion is 0.75 (0.59, 0.97).

Finally, there was no observed correlation between the within-study difference in mean temperature and result-
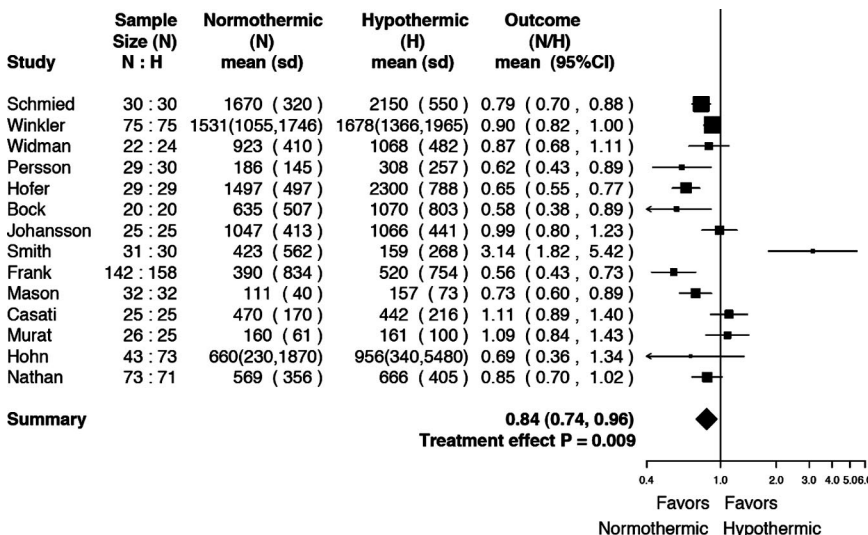

Fig. 1. Total blood loss meta-analysis and forest plot. Treatment effect is expressed as ratio of geometric means of blood loss for normothermic (N) *versus* hypothermic (H) patients. Results indicate an estimated 16% (95% CI 4%, 26%) lower average blood loss in normothermic *versus* hypothermic patients, $P = 0.009$.
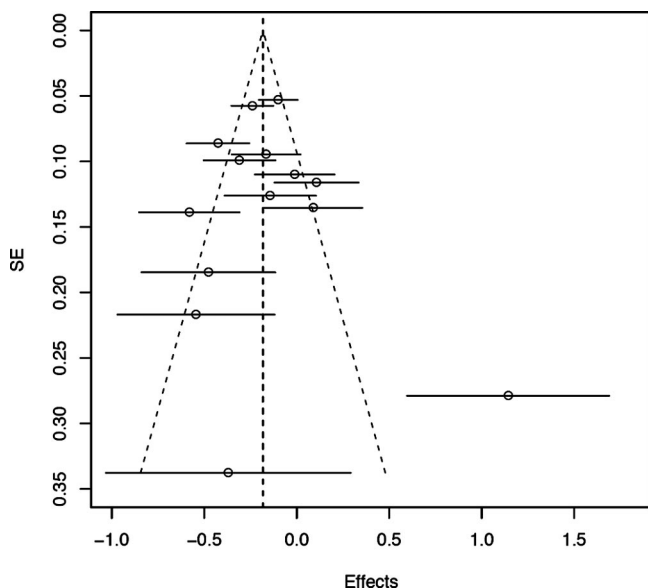
Fig. 3. Total blood loss funnel plot assessing publication bias. Plotted is the standard error (SE) *versus* the log treatment effect of each study. Vertical line is summary log treatment effect for blood loss (*i.e.*, log [0.84] = −0.17). Diagonal lines are expected 95% confidence interval (±1.96 SE) from the summary log treatment effect. Studies outside the funnel indicate heterogeneity. The fairly symmetric plot indicates low publication bias.

ing blood loss treatment effect, with correlation (95% CI) of −0.13 (−0.62 to 0.43), $P = 0.67$.

Discussion

A meta-analysis evaluating the effects of hypothermia on blood loss was required because many studies con-
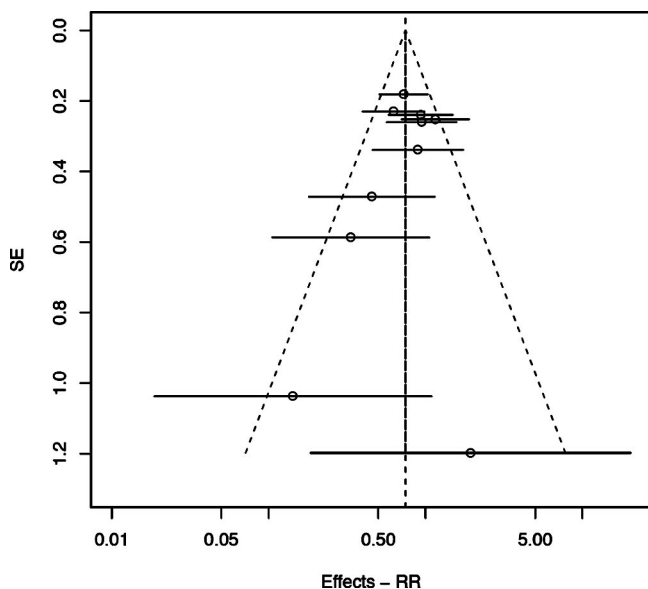

Fig. 4. Transfusion funnel plot assessing publication bias. Plotted is the standard error (SE) *versus* the relative risk (RR) of each study. Vertical line is summary relative risk (0.78). Diagonal lines are ±1.96 SE from the summary relative risk. The fairly symmetric plot indicates low publication bias.

clude that hypothermia impairs coagulation, whereas others conclude that it does not. Our analysis, based on available literature, indicates that even mild hypothermia significantly increases blood loss by an estimated 16% (CI 4–26%). Although not an enormous treatment effect, these data add to other studies that demonstrate that preventing hypothermia decreases the risk of many other complications and is thus indicated for reasons other than reducing blood loss.[7–14]

There is not a simple relationship between blood loss and transfusion requirement. Nonetheless, averaged across a sufficient number of patients and a variety of operations, increased blood loss presumably increases transfusion requirement. Our results are consistent with this theory: mild hypothermia significantly increased the relative risk for transfusion by approximately 22% (CI 3–37%). Reducing transfusion seems especially important now that increasing evidence suggests that transfusions are far more harmful than previously believed.[42–45] Our analysis was restricted to mild hypothermia (>34°C), but in fact, the median of the mean temperatures among studies for the patients assigned to hypothermia was approximately 35.6°C, which was only approximately a degree less than the median for the normothermic patients. Hypothermia in the studies we evaluated was thus of a magnitude that is typical for unwarmed surgical patients. Therapeutic hypothermia purposely induced to lower temperature will, presumably, produce yet greater impairment of coagulation.

Unwarmed patients undergoing larger and longer operations are more likely to become hypothermic than those having shorter and smaller procedures. They are also likely to lose more blood. Consequently, retrospective correlations between hypothermia and blood loss are especially likely to be confounded. We therefore restricted our analysis to prospective, randomized trials.

Blood loss and transfusion requirement were the primary outcomes for some of the articles included in our analysis.[23,24,30,31] However, coagulopathy was a secondary or even incidental finding in others.[9,26–29,32–35] This is an important distinction because potential confounding factors are usually only well controlled for the primary outcome. Secondary outcomes may also be suboptimally evaluated. Finally, secondary or incidental findings are often only reported when statistically significant; reported outcomes may thus overestimate the actual effect. Nonetheless, the effects of hypothermia were generally similar in studies in which blood loss and transfusion requirement were primary or secondary outcomes.

Although blood loss typically has a distribution quite skewed to the right and thus not normally distributed, many of the articles in this meta-analysis summarized it as mean ± SD and analyzed it using a *t* test, which assumes normality. However, from experience, it is clear

that blood loss is closer to the log-normal than the normal distribution, a fact that has been highlighted by others.[24,31] For our meta-analysis, we thus desired a summary mean ± SD for each study on the log-transformed scale so that our inference among studies would be more accurate than using nontransformed means and SDs. Assuming a log-normal distribution for the raw data, we used the formulae for the relationship between the nontransformed and transformed mean and SD of a log-normal variable to determine the estimated log-scaled mean ± SD for each study. These were then exponentiated (*i.e.*, back-transformed) to obtain the geometric means, and we report the ratio of geometric means as our outcome measure for each study and overall. Reporting the ratio instead of the difference in means allows intuitive comparison of studies with differing volumes of blood loss.

All meta-analyses are based on published results and thus subject to any methodologic problems in the underlying reports. This is not a trivial consideration: even using our relatively crude quality scoring, it is apparent that many of the articles we included failed to meet even the most basic elements of trial design. An additional limitation is publication bias. It is possible, perhaps even probable, that some "negative" results were never published either because the authors abandoned the project or because journals were reluctant to publish negative results. To the extent that this is the case, our analysis will overestimate the coagulopathy of hypothermia. Examination of funnel plots revealed some asymmetry, and thus mild evidence of publication bias, but not strikingly so. The blood loss treatment effects were found to be heterogeneous; this should not be considered a negative finding, but rather evidence that a thorough literature search was done, resulting in studies with wide ranges of effects. More subtle limitations of meta-analyses have been reviewed extensively.[46,47]

It is worth noting that there are many examples of meta-analyses that were proven false by subsequent large trials.[48,49] No meta-analysis, including this one, should be considered a substitute for very large (n >1,000) trials. A difficulty in this case, however, is that hypothermia is causally linked to numerous serious complications. Maintaining normothermia has thus become the standard of care; a consequence is that conducting a large trial in which patients are randomized to perioperative hypothermia would be ethically challenging.

In summary, our meta-analysis indicates that even mild hypothermia (<1°C) increases blood loss and the relative risk of transfusion by small but significant amounts. These data add to the evidence supporting maintenance of normothermia perioperatively.

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