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Nonsurgical Strategies to Reduce Mortality in Patients Undergoing Cardiac Surgery: An Updated Consensus Process

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Mortality reduction in cardiac anesthesia and intensive care: an updated consensus process.

INTRODUCTION

In the last decades, the improvement in surgical and anesthesia techniques led to a reduction in mortality among patients undergoing cardiac surgery [AP1, AP2]. Isolated cardiac interventions are generally perceived as relatively low-risk procedures but perioperative mortality is about 2%, 3%, and 4.3% for CABG, aortic valve replacement, and mitral valve replacement, respectively [AP3, AP4, AP5]. Furthermore, the number of elderly patients with comorbidities and poor preoperative functional status scheduled for multiple cardiac procedures is increasing [AP7, AP8, AP9, AP10].

Using a pioneering approach to consensus building, all non-surgical interventions (drugs, techniques, and strategies) with literature evidence of a significant effect on mortality were systematically identified and briefly assessed and described by the first international consensus conference on mortality reduction in cardiac anesthesia and intensive care [AP12]. Afterwards, this innovative consensus process, which was later called "democracy-based medicine" [AP13], has been refined and applied to different clinical settings, such as the perioperative period of any surgery [AP14, AP15], acute kidney injury [AP16], and critical care [AP17, AP18]. Here we present the results of the updated democracy-based, web-enabled consensus conference on mortality reduction in patients undergoing cardiac surgery.

METHODS

Cardiac anesthesiologists, cardiac surgeons, intensivists and cardiologists participated at this updated consensus conference in cardiac surgery mortality. They participated in person, through

email or through the congress web site.

MEDLINE/PubMed, Scopus, and Embase were searched by four investigators with no publication time limits and updated on 27 November 2015 to identify all randomized controlled trials (RCTs) and non RCTs of any non-surgical intervention reported to increase or decrease mortality in cardiac surgery patients (see Supplemental material for the full search strategy). The authors found additional articles through a cross-check of references and suggestions by experts in the field of perioperative medicine. Only studies that fulfilled all these criteria were accepted as valid for study inclusion: (a) study published in a peer-reviewed journal, (b) including ancillary (i.e. non-surgical) treatments (drug/technique/strategy) in patients undergoing cardiac surgery, (c) with a statistically significant reduction/increase in mortality. Difference in mortality was considered statistically significant when present at a specific time point (landmark mortality) with simple statistical tests and without adjustment for baseline characteristics.

The Consensus meeting was held on 27 November 2015 at the Vita-Salute University of Milan, Italy when all topics were discussed. Aims of the Consensus Conference were to establish whether: (a) the most recent evidence had been collected; (b) the reduction or increase in mortality was supported by either: randomized controlled trials (RCT) or meta-analyses of RCTs, case-matched studies, meta-analyses of case matched studies, or other studies; (c) the evidence had been derived from a subgroup or a primary analysis; (d) the evidence had been derived entirely or partially from cardiac-surgical population; and when among a cardiac surgical population, if it was applicable to every cardiac intervention or to certain subgroups only; (e) the drug/technique/strategy was used in the operative room or in an intensive care unit; and (f) mortality was the endpoint, or mortality was included in a composite endpoint.

Two experts, a rapporteur and a co-rapporteur, presented each intervention describing the reasons for it being considered as included, or excluded. Thus, for each topic included a final statements were created, discussed, and corrected during the conference.

Several studies were excluded on methodological grounds because of lack of reproducibility or

generalizability, low methodological quality, major baseline imbalances between intervention and control groups, major design flaws, contradiction by subsequent larger trials, modified intention-to-treat analysis, effect found only after adjustments, and lack of biological plausibility. The studies or interventions that did not meet the aforementioned criteria became major exclusions.

Through an interactive web questionnaire at http://www.democracybasedmedicine.org , participants had the opportunity to vote in support of or against the suggested topics (Table 1). We asked clinicians whether they agreed or disagreed with the validity of each intervention and whether they used or avoided each intervention in clinical practice. The following 3 questions were asked: Do you agree with this sentence? Do you routinely use this intervention in your clinical practice? Would you include this intervention into future international guidelines to reduce perioperative mortality? For the interventions increasing mortality, the second and third questions were asked in an opposite fashion: Do you routinely avoid this intervention in your clinical practice? Would you suggest that future international guidelines should contraindicate this intervention to reduce perioperative mortality? For each question the authors included the option "don't know" and "does not apply" in the questionnaire to allow respondents to state that they had no opinion on a particular issue or do not have the possibility to use a particular drug.

Because methodologic research suggests, as previously mentioned, (ref 6,8) that there is no difference in response rate depending on the inclusion or exclusion of the "do not know" option (if less than 40%), (ref 9) only the "yes" and "no" frequencies were reported in the results if not otherwise indicated.

After the web vote, the interventions that reached less than 67% of agreement were considered as major exclusions along with those excluded during the meeting, with details showed in table s1 and table s2.

The interventions with an impact on mortality that were approved after the web vote, with the references to the articles supporting the evidence, are reported in Table 2 if overwhelming evidence was not published thereafter.

Statistical Analysis

From the data provided in the articles, the relative risk reduction or increase, absolute risk reduction or increase, and number needed to treat or harm were calculated. The results of the web vote are expressed as percentage of positive votes. The percentage of agreement of the following data are reported: (1) selected literature; (2) use/avoidance in clinical practice; and (3) inclusion in future guidelines. Statistical analysis was performed using Stata13 software (Stata Corp, College Station, TX). The chi-square or Fisher exact test was used to evaluate differences in percentages among countries and specialists. Statistical significance was set at $p < 0.05$.

RESULTS

The web survey identified 10 topics that influenced unadjusted landmark mortality as life-saving: aspirin, glycemic control, high-volume surgeon, leuko-depleted red blood cell transfusion, levosimendan, non-invasive ventilation, prophylactic intra-aortic balloon pump, vacuum-assisted closure, volatile agents, and tranexamic acid. Aprotinin was identified as the only that increase mortality.

The sentences written by the experts during the consensus conference meeting held in Milan on the 11 interventions that reduced or increased mortality in cardiac surgery patients, according to the articles 1-33 are presented in table 1.

The 11 interventions selected using the web survey were supported by 33 (1-33) articles published between 1998 and 2015. The other details (journals, year, type of article) and the percentages of agreement of the web voters for the 33 articles with differences in mortality are reported in table 2.

The journals that published the 33 articles with differences in mortality are reported in Table 7.

Overall, 458 clinicians from different word's country participated in the web survey and more than 80% were anesthesiology or intensive care specialists (table 3).

The percentages of agreement were as high as 90%. The concordance between routine use of each drug/technique/strategy and agreement for the same type of intervention was reported in table 4.

The lowest concordance was for VAC (40%) and the highest was for glycemic control (83%).

The percentage of agreement among different group countries (table 5) was statistically different for 8 of the 11 interventions, with the lowest concordance seen for the topic "High-volume surgeon".

The concordance between routine use of each drug/technique/strategy and agreement for the same type of intervention for country was reported in table s3.

When comparing the opinions of anesthesiologists and intensive care specialists with other physicians about interventions reducing mortality, no statistically significant differences were observed (table 6). The concordance between routine use of each drug/technique/strategy and agreement for the same type of intervention for job was reported in table s4.

Major study exclusions were identified and are reported in Tables s1, with the reason for exclusion table s2).

Notably, 4 interventions that reached the final stage of the web vote were excluded because they did not reach the minimum general agreement set at 67%. One intervention (preoperative statin therapy in statin-naïve patients) was excluded after completion of the web vote because large, high- quality RCTs showing no benefit and possible harm were published thereafter. (REF A e B)

DISCUSSION

Key findings

We identified all ancillary (i.e. nonsurgical) interventions, including drugs, techniques or strategies, which have been shown by at least one study published in a peer-reviewed journal to significantly affect mortality in patients undergoing cardiac surgery. In particular, aspririn, glycemic control, high-volume surgeons, prophylactic intra-aortic balloon pump (IABP), levosimendan, leuko-depleted red blood cells (RBC) transfusion, non-invasive ventilation (NIV), tranexamic acid,

vacuum-assisted closure (VAC), and volatile agents might reduce mortality, while aprotinin likely increases mortality. Moreover, we analysed how these interventions were regarded by a large cohort of colleagues worldwide, and to what extent they translate into their clinical practice. Through a well-proven "democratic" consensus process which has been widely described previously [AP6, AP13-18], the systematic review of literature was filtered through the views and the experience of 458 clinicians from all around the World, allowing to draw up a pragmatic guide with strict adherence to evidence-based medicine (EBM) and intended to improve patients' survival and to direct future research.

This study also provides the opportunity to observe the existing gap between medical literature and clinical practice which has been already noticed in other perioperative and intensive care settings [AP15, AP18]. Furthermore, as an update of the consensus process conducted in 2010 [AP12], it allows to follow the evolution of EBM, pointing up the continuous need for high quality studies focused on major outcomes such as mortality in order to promptly update our beliefs and modify our clinical practice accordingly.

Relationship to previous literature

Firstly, it is interesting to compare the present findings with those of the first international consensus conference on mortality reduction in cardiac anesthesia and intensive care, which was held in 2010 and whose results were published in 2011 [AP12]. Unfortunately, the list of interventions which may save the life of patients undergoing cardiac surgery has not lengthened a lot. However, although the total number is similar (11 vs. 10), three of the 10 interventions which were previously included have been excluded in the present update (statins, beta-blockers, and old RBC transfusion), while four new interventions have been included (leuko-depleted RBC transfusion, tranexamic acid, NIV, and VAC). Most remarkably, the literature evidence of a significant effect on mortality has strengthened for all the seven topics included in both the

consensus conferences. For example, the survival benefit of aspirin, high-volume surgery, volatile agents, IABP, and levosimendan was supported by only one study for each topic at the time of the first consensus conference, while now the number of investigations reporting a significant reduction in mortality is 2 for aspirin, 3 for high-volume surgery and volatile agents, 6 for IABP, and 7 for levosimendan. Moreover, the number of interventions supported by randomized evidence (RCTs or meta-analyses including RCTs) is proportionally increased, leading to an overall increase in the level of evidence.

It is also interesting to note that, as compared with the similar consensus conference we conducted to identify the interventions that can affect mortality in the perioperative period of any (adult) surgery [AP14, AP15] and, especially, with that dealing with the critical care setting [AP17, AP18], the number of RCTs showing significant differences in mortality is much lower. In the perioperative setting, we identified 13 topics supported by 39 papers among RCTs and meta-analyses of RCTs [AP15], while in critical care even if we limited the search to multicentre RCTs (mRCTs) we were able to include 15 interventions supported by 24 mRCTs [AP17, AP18]. Conversely, although in cardiac surgery we extended our analysis to any kind of investigation, we only found 33 papers, only 9 of which are RCTs.

Remarkably, the comparison among the different consensus conferences also shows how the same therapeutic intervention can be beneficial in a clinical setting and harmful in another. For example, strict glycemic control has been found to be beneficial in the perioperative period (especially of cardiac surgery) and potentially harmful in critically ill patients. Moreover, although beta-blockers were included in the first consensus conference on cardiac surgery among the interventions which can improve survival, this topic has been excluded in the present update, mainly because randomized evidence suggests that only arrhythmias (but not mortality) are reduced by B-blockers administration in cardiac surgery, and the association between B-blockers and mortality in cardiac surgery is likely to be considered as a marker of good outcome rather than causative. Consistently, the initiation of B-blockers immediately before non-cardiac surgery has been even included among

the interventions which might increase mortality by the consensus conference on the perioperative period of any surgery [AP14, AP15].

Implications for clinical practice and future research

Anesthesiologists, intensivists and surgeons who care for patients undergoing cardiac surgery have many choices available about anesthetic techniques to use, drugs to administer (or avoid) perioperatively, mechanical circulatory support devices, respiratory care, and many other nonsurgical strategies to use. However, it is often unclear whether these decisions may improve survival of their patients. As discussed previously [AP15], although guidelines can provide helpful information about interventions that may affect mortality, they are often dispersive and not always strictly adherent to EBM. The consensus process described here allowed to list together all interventions for which there is sufficient, non-conflicting and widely agreed evidence of an effect on mortality in the field of cardiac anesthesia and intensive care.

Our findings also confirm the existence of a wide gap between literature evidence and clinical practice, as well as of significant differences in both beliefs and clinical practice among different countries, as already found in other settings [AP15, AP18]. In fact, despite the percentage of agreement was above 80% for 9 out of 11 interventions affecting survival, the consistency between agreement and use in clinical practice was most often lower than 70%. In most cases, the differences among countries concerned not only the use in clinical practice, but also the agreement itself with the usefulness of the interventions in terms of patients' survival.

Evidences bringing relatively new "messages" such as liberal transfusion strategy and dexmedetomidine were excluded (see Supplemental table 2) due to low agreement, suggesting that adequate time is needed by clinicians to "digest" literature evidence but, maybe, also that there is an increasing tendency to cautiously beware literature evidences and wait for further proofs before changing clinical practice.

If the present list cannot be regarded, of course, as a "Decalogue" of interventions which definitely and undoubtedly improve survival among patients undergoing cardiac surgery, our findings may hopefully contribute to direct future research and to help (and speed up) the translation of widely agreed evidence into clinical practice.

Strengths and limitations

The strengths, in the authors' opinion, of such an approach to consensus building have been discussed many times [AP14-AP18]. In the present study, in particular, we focused on cardiac anesthesia and intensive care to summarize EBM dealing with a key outcome such as mortality. All interventions included are adherent to the real beliefs and clinical practice of clinicians and may represent a pragmatic guide for all colleagues worldwide and, especially, a hint to identify priority targets for future research. Indeed, the topics which were identified by the first international consensus conference on mortality reduction in cardiac anesthesia and intensive care [AP12] and confirmed in the present updated have an increased number of investigations in support of their role in affecting mortality.

However, if on the one hand, our analysis of consistency between agreement and use/avoidance confirms that clinical practice often adapts slowly to evidence, on the other hand our findings suggest that, quite surprisingly, also research itself moves rather slowly in a field which is characterized by high complexity and morbidity and by an in increasing level of risk.

A limitation of the present study is certainly the overall rather low level of evidence of the included topics which, together with the continuous evolution of evidence, does not allow to draw, in most cases, definitive conclusions. For example, although a moderate bulk of evidence has accumulated in the last five years about the role of levosimendan on mortality among cardiac surgery patients, we are eagerly waiting for the results of the large RCTs LICORN (NCT02184819, France), CHEETAH (HSR-LEVO) [AP19], and LEVO-CTS [AP20], which might subvert our actual beliefs.

As in the previous consensus conferences, we have not investigated the reasons of the differences among countries or of the gap between agreement and clinical practice. However, this was not the scope of the present study and would have affect the simplicity and agility of our web-based voting process, which in our opinion is also a strength. Other limitations in common with the previous consensus conferences conducted by our group included, as discussed earlier [AP15], the lack of details about the included interventions, which are only listed and very briefly contextualized.

CONCLUSIONS

This updated international web-based consensus conference process identified eleven interventions supported by widely agreed evidence suggesting their impact on mortality among patients undergoing cardiac surgery. The analysis of web voting confirmed that there is a gap between evidence and clinical practice and that both the perception of literature evidence and the clinical attitude of cardiac anesthesiologists and intensivists are significantly different among different countries for many of the included interventions. Future research should be addressed to a better definition of the role of these interventions, as well as of major exclusions, and to investigate the possible means to reduce both the gap existing between evidence and clinical practice and the differences among different countries. Hopefully, at least the interventions supported by the strongest evidence should be included into international guidelines on the perioperative care of patients undergoing cardiac surgery.

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