Evidence-Based Medicine: Principles and Values as Illustrated by the Case of Patient Blood Management

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Hamostaseologie 2023;43:16–21.

Abstract

Evidence-based medicine is considered 1 of the 15 great inventions in medicine. It aims to remove bias in medical decision-making as much as possible through a rigorous process. In this article, the principles of evidence-based medicine are illustrated using the case of patient blood management (PBM). Acute or chronic bleeding, iron deficiency, and renal and oncological diseases may lead to preoperative anemia. To compensate for severe and life-threatening blood loss during surgery, doctors transfuse red blood cells (RBCs). PBM is an approach to take care of patients at risk for anemia, which includes detecting and treating anemia before surgery. Alternative interventions to treat preoperative anemia are the use of iron supplementation with or without erythro-stimulating agents (ESAs). The best available scientific evidence today indicates that preoperative intravenous (IV) or oral iron monotherapy may not be effective to reduce RBC utilization (low-certainty evidence). Preoperative IV iron supplementation in addition to ESAs is probably effective to reduce RBC utilization (moderate-certainty evidence), whereas oral iron supplementation in addition to ESAs may be effective to reduce RBC utilization (low-certainty evidence). The adverse events of preoperative oral/IV iron and/or ESAs and their impact on patient-important outcomes (morbidity, mortality, quality of life) remain unclear (very low-certainty evidence). Since PBM is a patient-centered approach, emphasis on monitoring and evaluation of patient-important outcomes in future research is urgently needed. Finally, the cost-effectiveness of preoperative oral/IV iron monotherapy is unproven, whereas preoperative oral/IV iron in addition to ESAs is extremely cost-ineffective.

Keywords
- evidence-based medicine
- patient blood management
- anemia
- erythro-stimulating agents
- iron supplementation

Zusammenfassung

Die evidenzbasierte Medizin gilt als eine der 15 großen Entdeckungen in der Medizin. Hintergrund ist, medizinische Entscheidungen durch strenge und transparente

received
October 14, 2022
accepted after revision
November 22, 2022

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-1985-7660.
ISSN 0720-9355.

Prozesse ohne „Bias“ treffen zu können. In dieser Arbeit werden die Prinzipien der evidenzbasierten Medizin am Beispiel des Patient Blood Management (PBM) beleuchtet.

Akute oder chronische Blutungen, Eisenmangel, Nieren- oder Krebserkrankungen können zu einer präoperativen Anämie führen. Um einen schweren und lebensbedrohlichen Blutverlust während Operationen auszugleichen, werden üblicherweise Erythrozyten durch die Gabe von Erythrozytenkonzentraten (RBCs) transfundiert. PBM ist ein Ansatz zur Behandlung von Patienten mit einem Risiko für Blutverlust und/oder Anämie, der die Diagnose und präoperative Anämiebehandlung miteinschließt. Alternative Maßnahmen neben der Transfusion von Erythrozytenkonzentraten, um eine präoperative Anämie zu behandeln, sind die Substitution von Eisen mit oder ohne Erythropoese-stimulierenden Substanzen (ESAs). Unter bestmöglichen wissenschaftlichen Evidenzkriterien zum jetzigen Zeitpunkt ist die präoperative intravenöse (i.v.) oder orale Eisenmonotherapie nicht geeignet, den Bedarf an Erythrozytentransfusionen zu senken. Dem entgegen ist die kombinierte i. v. Eisensubstitution mit ESAs wahrscheinlich geeignet, die Erythrozytentransfusionsrate zu reduzieren, währenddessen dies für die Gabe der oralen Eisensubstitution zusammen mit ESAs nur sein kann. Dabei ist unklar, inwiefern unerwünschte Wirkungen/Nebenwirkungen der präoperativen Gabe oralen oder i. v. Eisens und/oder die Gabe von ESAs sich auf die Behandlungsergebnisse der Patienten wie z. B. Mortalität, Morbidität, Lebensqualität auswirken. Da PBM eine personalisierte Vorgehensweise der Behandlung ist, ist zukünftig eine Gewichtung der Forschung auf Monitoring und Evaluation der für den einzelnen Patienten wichtigen Behandlungsergebnisse erforderlich. Von wesentlicher Bedeutung ist die wirtschaftliche Bewertung von PBM-Maßnahmen: Während der Kosten-Nutzen-Effekt der präoperativen Eisenmonotherapie (oral/i. v.) nicht belegt ist, ist auf Basis der Evidenz die präoperative orale/i. v. Eisengabe zusätzlich zu ESAs extrem unwirtschaftlich.

Schlüsselwörter

- evidenzbasierte Medizin
- Patient Blood Management
- Anämie
- Erythropoese-stimulierende Substanzen
- Eisensupplementation

Introduction

Patient blood management (PBM) is “an evidence-based, multidisciplinary approach aimed at optimizing the care of patients who might need a transfusion. PBM encompasses all aspects of patient evaluation and clinical management surrounding the transfusion decision-making process, including the application of appropriate indications, as well as minimization of blood loss and optimization of patient red cell mass. PBM aims to reduce the need for allogeneic blood transfusions and reduce healthcare costs while ensuring that blood components are available for the patients who need them. PBM puts the patient at the heart of decisions made around blood transfusion, promoting appropriate use of blood and blood components, and the timely use of alternatives where available.”[1,2]

In a recent publication, an expert group representing different PBM organizations proposed using a common and clear definition for PBM aiming to improve implementation and informed decision-making with the patient. They defined PBM as a “patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient’s blood while promoting patient safety and empowerment.”[3]

The terms “patient-centered” and “patient outcomes” clearly indicate PBM’s central philosophy and focus, namely individualizing care for the patient and making and delivering a plan to optimize their care. This plan may, or may not, involve transfusion, but avoiding unnecessary transfusions is not primarily what drives PBM. Therefore, improved patient outcomes (quality of life, quality-adjusted life years [QALY], and reduced morbidity and mortality) serve as the important primary outcomes of PBM.

In this article, PBM pertains to the management of anemia in the perioperative phase.

Evidence-Based Medicine

Expert opinion and personal experience have long been the main foundation for decision-making in health and health care. Gradually, between the 1950s and 1990s, the importance of scientific methods, testing hypotheses in controlled studies, and using statistical analyses became more apparent, and it became clear that medical decisions were too often dependent on individual opinions and practices, which sometimes led to harmful outcomes.[4–6]

This led to the introduction of the term “evidence-based medicine” (EBM) in 1991, defined as the integration of the

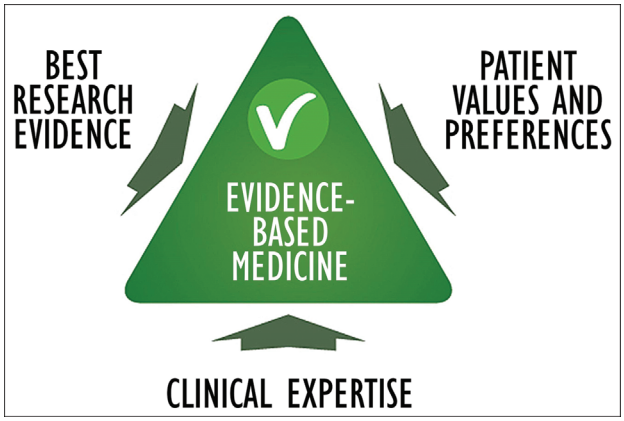

Fig. 1 The three dimensions of evidence-based medicine.

best research evidence with clinical expertise and patient values (►Fig. 1).[7,8] Since then and up until the beginning of the 2000s, the number of medical articles referring to EBM has increased exponentially, and today EBM is widely used in medical decision-making.

When it comes to operationalizing the definition of EBM, the first and most resource-intensive step is to systematically collect and analyze the "best available evidence" (i.e., of the highest quality). To use the "best evidence," the Hierarchy of Evidence was established to guide researchers when evaluating the quality of trials based on the likelihood that the methods used and the results obtained would be less prone to bias and their data more reliable. The study type of the highest quality is a systematic review (with meta-analyses) (►Fig. 2).

The hallmark of a systematic review is to avoid or reduce bias at every stage of the review process, that is, formulating the research question (in the so-called PICO [population–intervention–comparison–outcome] format), developing a search strategy for different scientific databases, selecting studies that fulfill the predefined selection criteria, extracting the data, assessing the risk of bias of the studies, and synthesizing the data, if possible in a meta-analysis.[9] The very systematic way of running through the different steps makes results as objective as possible (unlike "narrative reviews," which are rather subjective). In addition, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and many journals ask that each step is documented carefully, making each step transparent to and reproducible by readers and users of the review.[10] This allows decision-makers to assess the trustworthiness and applicability of review findings. This first step of EBM requires skilled and educated researchers or professionals,[11] and is a time-intensive step. The estimated average time to conduct a systematic review would range between 6 and 18 months.[12]

The second and third pillars of EBM, clinical expertise, and patient values can be integrated already during the development of systematic reviews, for example, by involving clinical experts in formulating the research questions and selection criteria. Further input from clinical experts and patients is sought to translate evidence into practical recommendations, forming an "evidence-based guideline." This process can be guided by GRADE's Evidence-to-Decision framework, taking into account the certainty of the evidence, benefits, harms, costs, and preferences of the target group.[13,14] Formally collecting expert opinion can be challenging, and many methods have been used, going from informal consensus building (e.g., during an expert meeting) to using formal structured methods such as Delphi methods or a consensus conference methodology.[15]

The introduction of evidence-based methodology has been nominated as 1 of the 15 most important medical milestones since 1840 by the *British Medical Journal*, in addition to, among others, the use of antibiotics, immunization, sanitation, and radiology.[16] In 2009, the Institute of Medicine stated that by 2020, 90% of clinical decisions would be covered by accurate, timely, and up-to-date clinical information and evidence-based guidelines.[17] It is not clear today if that goal has been reached; however, EBM is currently being used widely in many healthcare disciplines.

This article will provide an overview of evidence-based principles applied to the concept of PBM.

International Consensus Conference on Patient Blood Management 2018 (ICC-PBM 2018)

Since "evidence-based" is explicitly included in the PBM definition, it is key to use the EBM principles in the

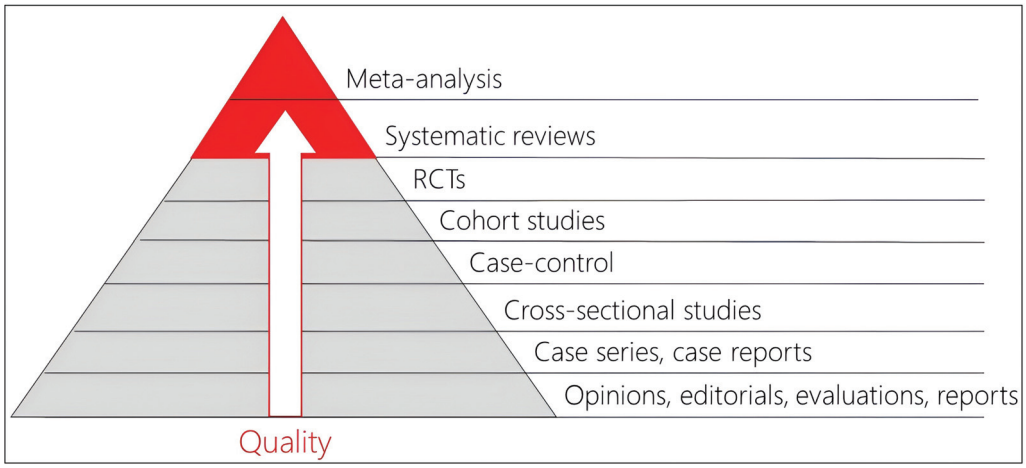

Fig. 2 The hierarchy of evidence.

formulation of evidence-based and clinically relevant recommendations.

The EBM principles were used during the ICC-PBM in 2018 (Frankfurt, Germany, initiated, chaired, and organized by Prof. Dr. Erhard Seifried), which aimed to formulate evidence-based clinical recommendations in three focus areas of PBM: preoperative anemia, RBC transfusion thresholds, and implementation of PBM programs. Systematic reviews on 17 PICO questions were conducted by a scientific committee (22 international topic experts and one methodologist). Based on the conclusions of these systematic reviews, plenary sessions (with 100–200 stakeholders from a range of clinical disciplines and community representatives) were followed by closed sessions, where multidisciplinary decision-making panels (>50 experts and patient organizations) used GRADE's Evidence-to-Decision framework to formulate 10 evidence-based recommendations on PBM.[18]

In the focus area "management of preoperative anemia," two conditional recommendations were formulated to consider the preoperative administration of iron monotherapy or iron supplementation in addition to short-acting ESAs, to reduce the RBC transfusion rate, in adult patients (with iron-deficient anemia) undergoing (major orthopaedic) elective surgery.[19] A conditional recommendation is one for which the guideline panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs. The reasons for the ICC-PBM guideline panel for not being confident in these two conditional recommendations on iron with or without ESAs were the absence of high-quality evidence. Additionally, the benefit was considered low (potential reduction in RBC units transfused), while the risks (e.g., thromboembolic deep vein thrombosis) were considered potentially life-threatening. However, the panel also noted that the probability of RBC transfusion, the etiology of anemia, and the thromboembolic risk of each individual patient must be considered since the relative benefit is balanced by a potentially life-threatening complication.

Evidence reviews with relevant RCTs (published until January 2018) were executed and the underlying evidence to these recommendations were (pooled) data from 3 RCTs (iron monotherapy) and 17 RCTs (iron + ESAs), showing a reduction in RBC utilization after preoperative iron and/or ESAs, compared with placebo and/or standard of care. Evidence about the effectiveness of preoperative iron/ESAs on patient and clinically important outcomes, such as morbidity, mortality, and quality of life, was lacking and could therefore not be used to scientifically underpin these recommendations. Furthermore, evidence about the cost-effectiveness (e.g., cost per QALY) of preoperative iron and/or ESAs was not considered. However, the cost-effectiveness of interventions is a key domain to consider when formulating recommendations for interventions.[20]

Lacking data on patient-important outcomes and the absence of cost per QALY data can be considered important limitations to these ICC-PBM 2018 recommendations (cfr. PBM definition).

The (Cost-)Effectiveness and Adverse Events of Preoperative Iron Supplementation and/or ESAs

To further scientifically underpin the ICC-PBM recommendations, three systematic reviews were conducted after the consensus conference, according to the predefined methodological standards of the Cochrane collaboration,[21] and by the PRISMA guidelines.[10] These systematic reviews identified the best available and up-to-date evidence (until November 2020) regarding the following PICO question:

In patients with preoperative anemia undergoing elective surgery (Population), is the use of iron supplementation with or without ESAs (Intervention), compared with placebo, standard of care, or no treatment (Comparator), effective to reduce RBC utilization, linked to adverse events and cost-effective (Outcomes)?

The Effectiveness of Preoperative Iron/ESAs on RBC Utilization

This systematic review found that IV iron monotherapy may not reduce the number of patients transfused (pooled RR: 0.65, 95% CI: 0.31–1.35; $p = 0.25$; 3 RCTs; low-certainty evidence). The evidence is very uncertain about the effect of oral iron monotherapy on the number of patients transfused (pooled RR: 0.53, 95% CI: 0.25–1.13; $p = 0.10$; 2 studies; very low-certainty). The magnitude of effect of iron monotherapy, compared with placebo or usual care, on the number of RBC units, transfused varied, ranging from no statistically significant effect in the PREVENTT trial (30 days: MD, −0.04; 95% CI, −0.27 to 0.19; $p = 0.74$; 6 months: MD, −0.15; 95% CI, −0.49 to 0.19; $p = 0.38$) to fewer units that were transfused in 2 smaller trials (median difference: 1.5–2 units lower; $p < 0.05$). The overall certainty of the evidence was considered as low.[22]

Oral iron + ESAs probably results in a reduced number of patients transfused (RR: 0.55, 95% CI: 0.41–0.74, $p < 0.00001$, 14 studies; moderate-certainty evidence) and the number of units transfused (MD: −0.69, 95% CI: −1.01 to −0.37, $p < 0.0001$; moderate-certainty evidence). IV iron + ESAs may result in a reduced number of patients transfused (RR: 0.67, 95% CI: 0.49–0.92, $p = 0.01$, 5 studies; low-certainty evidence).

Effectiveness of Preoperative Iron/ESAs on Patient-Important Outcomes

A systematic and standardized collection, measurement, documentation, and reporting of side effects of preoperative iron and/or ESAs and its impact on clinical and patient-important outcomes (such as morbidity, mortality, and quality of life) is lacking among the 26 RCTs and 16 included cohort studies (very low-certainty evidence). This prevented us to formulate any conclusions on the side effects and impact of preoperative iron + ESAs on clinically important outcomes.[23]

The Cost-Effectiveness of Preoperative Iron/ESAs

One economic evaluation investigated the cost-effectiveness of preoperative IV iron monotherapy (ferric carboxymaltose) in anemic patients undergoing orthopaedic surgery. The incremental cost per transfusion avoided and per allogeneic RBC unit transfused avoided was 831€ (range: 606–6,894) and 405€ (range: 296–16,465), respectively. Since only one study looked into the cost-effectiveness of preoperative administration of IV iron monotherapy, and this study had a limited time horizon/perspective (in-hospital only), the cost-effectiveness of preoperative oral/IV iron administration remains unclear due to a lack of data.

Four studies on the cost-effectiveness of preoperative ESAs in combination with oral iron administration were identified: two cost-effectiveness analyses, one cost–utility analysis, and one RCT. Three of these studies developed a model with a lifetime horizon and used a healthcare perspective. Despite different contexts (North America vs. Europe), patient populations (coronary vs. orthopaedic surgery patients), and cointerventions (preoperative autologous blood donation vs. none), the overall conclusions of these assessments were similar: routine use of preoperative ESAs and oral iron to correct anemia in elective surgery patients cannot be considered cost-effective, with costs per (quality-adjusted) life-year gained of several millions in the most realistic scenario according to the study authors. These conclusions were confirmed by re-running this model with up-to-date effectiveness data and by using recent cost data of ESAs, iron, and blood products.[24]

Comparison with Other Recent Systematic Reviews and Meta-analyses

Seven recently published systematic reviews with meta-analyses of RCTs answered a similar PICO question and confirmed our conclusions regarding no effect of preoperative iron monotherapy[25–28] or a reduced effect of ESAs in addition to oral/IV iron supplementation on blood transfusion rate.[29–31]

On the contrary, one review found that IV iron supplementation is associated with a significant decrease in blood transfusion rate in both anemic and nonanemic patients undergoing major elective surgery.[32] However, the data of the PREVENTT trial[33] were not in the meta-analysis of this review, because this trial was ongoing at the time this review was conducted. Otherwise, also this review would have confirmed the first seven reviews.

Three other recent systematic reviews synthesized the adverse events, including the impact on clinically important outcomes, of oral/IV iron supplementation with or without ESAs in patients with preoperative anemia undergoing elective surgery. These reviews found no statistically significant difference in complications and 90-day mortality,[29] no important differences in the risk of adverse events (e.g., renal dysfunction, thromboembolism, hypertension, allergic reaction, headache, fever, constipation), or mortality within 30 days.[31] Another systematic review and meta-analysis of 154 RCTs found that intravenous iron was associated with an increased risk of infection when compared with oral iron or no iron (RR: 1.17, 95% CI: 1.04–1.31, moderate certainty-evidence) and there was no evidence of an effect on mortality.[34] These systematic reviews recommended more future research including larger well-designed longer-term RCTs with robust methodology and standard definitions of adverse events to estimate the safety of iron + ESAs more precisely to understand the balance between risks and benefits.

Finally, no other SRs identified other full economic evaluations investigating the cost-effectiveness of iron with or without ESAs in anemic patients undergoing elective surgery.

Conclusions

EBM is a powerful tool to make health-related decisions based on the integration of the best available scientific evidence with clinical expertise and patient values.

When applied to PBM, our systematic reviews identified the best available evidence about (cost-)effectiveness of preoperative iron and/or ESAs in patients with anemia undergoing elective surgery and concluded that (1) preoperative IV or oral iron monotherapy may not be effective to reduce RBC utilization (low-certainty evidence); (2) preoperative oral iron supplementation in addition to ESAs is probably effective to reduce RBC utilization (moderate-certainty evidence); (3) preoperative IV iron supplementation in addition to ESAs may result in a reduced number of patients transfused (low-certainty evidence); (4) the adverse events of preoperative iron and/or ESAs and their impact on patient-important outcomes (morbidity, mortality, quality of life) remain unclear (very low-certainty evidence); (5) the cost-effectiveness of preoperative oral/IV iron monotherapy is unproven, whereas preoperative oral/IV iron + ESAs is extremely cost-ineffective.

The future research agenda on preoperative anemia management should focus on the systematic collection, measurement, documentation, and reporting of the adverse events of preoperative oral/IV iron with or without ESAs and its impact on patient-important outcomes, as patient values is an important pillar of the EBM methodology, and PBM is a patient-centered approach. In addition, future economic evaluations with up-to-date cost, efficacy, and safety data are needed to estimate the cost per QALY for preoperative iron administration in patients with anemia.

Since PBM is a systematic, evidence-based, patient-centered approach, these future research studies should be highly prioritized because guideline developers will consider patient-important outcomes (morbidity, mortality, quality of life) as the primary outcomes of interest when formulating recommendations. Future international PBM guideline initiatives are needed to translate the best available scientific evidence (EBM dimension 1) with the preferences and values of the transfused patient (EBM dimension 2), and the clinical expertise (EBM dimension 3).

Funding/Acknowledgment

This work was made possible through funding from the Foundation for Scientific Research of the Belgian Red Cross.

Conflict of Interest

The authors declare that they have no conflict of interest.

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