Enhanced recovery after elective surgery. A revolution that reduces post-operative morbidity and mortality

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Enhanced rehabilitation after scheduled surgery. A revolution that reduces post-operative morbidity and mortality

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Summary

Enhanced recovery after scheduled surgery (ER) *(I think ERAS should be avoided because it has become a trademark-AF)* has been a real revolution in peri-operative care. This concept, initially called "fast-track surgery", has evolved into "enhanced recovery or rehabilitation" (ER), which highlights the improvement of post-operative procedures rather than the simple shortening of hospital stay. The main benefit of ER is the reduction of the impact of surgical trauma with an attendant reduction of post-operative complications. This result has been demonstrated based on a good level of evidence for multiple surgical specialties. Mild complications are the most impacted by this program. The reduction in the duration of stay is thus the result of the improvement in post-operative care. This update illustrates the benefits of ER by taking three examples of scheduled surgery in three major surgical specialties: colorectal surgery, orthopedics and gynecological surgery. The post-operative complications impacted by ER programs and the mechanisms of this effect are also discussed.

Keywords: Enhanced rehabilitation after surgery, Post-operative complications, Colorectal surgery, Gynecological surgery, Orthopedic surgery

1. Introduction

The broad surgical community (surgeons and anesthesiologists) is experiencing a veritable revolution in peri-operative care, throughout all specialties. This revolution is based neither on technological (like robotic surgery) nor on

pharmaceutical innovations, but on organization of care. Enhanced recovery programs (ER) have become the standard of care in several surgical specialties, mainly for so-called major surgery. This is the second revolution (after laparoscopy) in the history of modern surgery [1]. It is indeed rare for any innovation to result in such a marked improvement in post-operative care.
The ER program includes three phases of pre, per- and post-operative care and employs technical measures that are applicable to all surgical specialties as well as measures specific to each specialty. There is, *a priori,* no contraindication to ER programs but the protocols are adapted to particular cases of patients (elderly patients, diabetics, *etc*.) or to conditions of care (emergency surgery). Even an incomplete ER program is better than no ER at all. Taking the example of scheduled colorectal surgery, the ER program is comprised of around twenty measures, in which the laparoscopic approach plays a preponderant role, as demonstrated by the LAFA trial [2]. However, when laparoscopy is contraindicated or must be converted to laparotomy, the other measures are still highly recommended (and laparotomy is not in contradiction with ER). It has been shown that the success of ER programs increases as the maximum of measures are applied.
The purpose of ER is not simply to "get patients out of the hospital quickly." Its purpose is to improve the aftermath of the surgery.

2. From "fast-track" to ER

In the early 1990s, accumulated scientific data on surgical aggression enabled American researchers [3] and the team of Henrik Kehlet [4] to propose a protocol called "fast-track surgery").
In the mid-2000s, clinical research demonstrated a new benefit of ER: the improvement of post-operative course in terms of patient comfort and overall morbidity. The concept has thus evolved into "enhanced recovery after surgery", and emphasizes that the shortening of the length of stay is only the result of the improvement of the post-operative course.

3. ER reduces overall morbidity

A bibliographic search of PubMed in December 2019 using the keywords "enhanced recovery after surgery" or "fast-track surgery" identified for all specialties combined one hundred systematic reviews or meta-analyses that constitute the best level of evidence. It would be tedious to list them all in the references for this article. We have chosen to look at scheduled surgery in three specialties: colorectal surgery, orthopedic surgery and gynecological surgery (which represent the largest volume of surgical procedures benefiting from ER). This study is limited to meta-analyses that satisfy the PRISMA criteria [5].

a) Colorectal surgery

Among the seven meta-analyses that compared ER to traditional management, six included between two and seven randomized trials and one included 13 [6] with a combined total number of 1910 patients. This last meta-analysis [6] has a good methodological quality.

The results of this meta-analysis (Table 1) supersede those of the previous meta-analyses because they summarize the literature on the place of ER in colorectal surgery. This meta-analysis clearly shows (and with a good level of evidence) that ER reduces overall morbidity by almost 40%, essentially by reducing non-surgical complications, without increasing re-hospitalization. There was no difference in mortality.

These results are global for all scheduled colorectal surgery *(I have no idea what he means?? The sentence has no meaning for me-AF).* The only weakness of this meta-analysis is the lack of subgroup analysis on rectal surgery. The benefits of ER programs for rectal surgery have not yet been demonstrated in studies of good methodological quality.

On the other hand, beyond the benefit of shortened duration of hospital stay, the benefits of colorectal ER in terms of post-operative morbidity were also demonstrated in elderly patients in two randomized trials [7,8].

b) Hip and knee surgery

There is widespread enthusiasm for ER among orthopedic surgeons. Orthopedic surgery comprises the main contingent of patients included in the French-speaking GRACE-Audit database (n = 16,112 in December 2019). However, unlike colorectal surgery, only two meta-analyses have been published. We will retain the most recent [9] because it included a larger number of studies (n = 25) and of patients (n = 16,699). This meta-analysis showed a 26% reduction in overall morbidity, a 56% reduction in transfusions and, above all, a halving of mortality. All reductions were statistically significantly in favor of ER (Table 2).

c) Gynecological surgery

Data on ER for gynecologic surgery are scarcer in the literature and have a lower level of evidence. A meta-analysis [10] has been published on various interventions by laparotomy (mostly hysterectomies). This is one meta-analysis of non-randomized studies with several confounding factors and probable patient selection. As an indication, this meta-analysis showed a similar overall morbidity rate at 30 days ($p = 0.94$) and a similar re-admission rate ($p = 0.59$) after ER or conventional treatment. More recently, two randomized trials [11,12] were published and did not show a difference in favor of ER, but the small size of these trials (62 and 103 patients, respectively) leads us to strongly fear a type-2 error (wrongly concluding that there is no difference).

These three examples illustrate well the diverse situations of practices and the literature. In the first case (colorectal surgery), the data are robust showing a reduction of complications by almost half for patients with ER; for orthopedic surgery, the data are fairly robust in favor of ER with an additional benefit not

found in other specialties: the reduction of post-operative mortality. And in the third case (gynecologic surgery) The level of evidence is low for reports of ER for gynecologic surgery and represents only very early experience.
Lower overall morbidity associated with ER has also been demonstrated with a good level of evidence, in other specialties such as hepatic, esophageal, pancreatic, gallbladder, pulmonary, and vascular surgeries.

4. What types of morbidity are impacted?

The most significant benefit of ER concerns so-called "non-surgical morbidity". Most of the factual evidence concerns colorectal surgery. Other studies in different specialties have been published but they are mostly heterogeneous and do not allow the question to be answered for all specialties with a good level of evidence. The answer will certainly come as ER is disseminated throughout these specialties and from the studies currently in progress.

a) ER reduces mild complications

The benefits of ER are essentially a reduction in Clavien-Dindo grade 1 or 2 morbidity [13] (moderate morbidity), such as post-surgical urinary, respiratory or ileus complications [14,15]. A beneficial effect of ER on more severe morbidity (Clavien-Dindo grade ≥3) is observed when ER programs are optimally implemented (≥90% of measures) [16].

b) ER reduces nosocomial infections.

By reducing potential entry portals for infection (catheters, drains) and decreasing surgical trauma, ER could lead to fewer healthcare-associated infections. A meta-analysis published in 2017 [17] has confirmed this hypothesis. The meta-analysis included 36 studies (41 comparisons) in several specialties: mainly colorectal surgery (n = 26), gastrectomy (n = 7), repair of abdominal aortic

aneurysm (n = 2), hepatectomy (n = 2), bowel surgery (n = 2), esophagectomy (n = 1), and prostatectomy (n = 1). The absence of studies in orthopedics is notable. Meta-analysis found that ER was associated with a statistically significant reduction in pulmonary infections (-62%, $p < 0.0001$), urinary tract infections (-58%, $p < 0.004$), and, to a lesser degree, surgical site infections (-25%, $p < 0.04$). The predominant number of studies on colorectal surgery makes these results especially valid for this specialty.
This meta-analysis suggests, with a good level of evidence, that ER would be an effective and inexpensive way to reduce nosocomial infections.

5. Possible mechanisms

Any surgical procedure constitutes a pathophysiological attack on the patient's body, all the more so because it also involves associated anxiety, prolonged fasting, bleeding, hypothermia, variations in blood volume, pain, hypoxia, bed rest, ileus, and/or cognitive disorders. The responses to this surgical stress are complex involving the release of various inflammatory mediators and, above all, insulin-resistance resulting in hyperglycemia, which plays a major role in surgical trauma and the development of complications [18].
The effects of surgical trauma are particularly marked in certain groups of patients whose homeostasis is already weakened by their co-morbidities: the elderly, diabetics and cancer patients [19]. By reducing surgical aggression and its deleterious effects, ER contributes to the reduction of post-operative complications.

6. Which comes first, the chicken or the egg?

It is conventional to consider that certain post-operative measures (early mobilization and early re-feeding) are factors in reducing post-operative morbidity, but the literature provides little evidence [20]. We do not know, in the current state of knowledge on ER, whether patients have fewer complications

because they leave their bed quickly and resume eating quickly or if these effects are due to their not developing a post-operative complication: this is the old story "of the chicken and the egg" [21]. Thus, it could be considered that, like post-operative morbidity or length of hospital stay, early mobilization and well-tolerated early resumption of diet could be markers rather than post-operative elements of the ER protocol. They would thus reflect an optimal implementation of pre- and post-operative measures. A recent study of the GRACE database involving several thousand patients undergoing colorectal surgery showed that poor tolerance of early re-feeding (on D1) was a warning sign of future post-operative morbidity (with an odds ratio of 4.5) [22].

7. Importance of the pre- and intra-operative phases

We can then wonder if it is not the pre- and intra-operative measures that most influence post-operative follow-up, convalescence, recovery and the occurrence of complications. Venara *et al.* have also shown the role of certain inflammatory mediators measured intra-operatively on the post-operative course and the occurrence of ileus [23].

Among the pre-operative measures, rehabilitation (physical, cardiorespiratory, musculoskeletal, nutritional, and psychological multimodal therapy) will not be detailed here. These are, at the present time, reserved for special cases such as elderly or frail patients. Their effect on post-operative morbidity and mortality has not been indisputably proven.

Table 3 summarizes the essential measures that have been shown (with a good level of evidence) to have an impact on post-operative morbidity and mortality.

8. Conclusions

The impact of ER on overall post-operative morbidity has been demonstrated in several clinical situations, but certainly unevenly. The riskier the surgery (colorectal surgery, major digestive surgery, surgery on fragile patients) the more

useful the ER. ER has been shown to have a beneficial impact on mortality in certain situations such as orthopedic surgery. The reduction of nosocomial infections is a benefit that should not be overlooked.

Beyond its benefits for morbidity and mortality, ER is beneficial for convalescence, the length of post-operative hospitalization, patient satisfaction, and the cost of care. Finally, we would note that there are very few examples in the recent history of medicine where an evolution of care management has led to such dramatic results.

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	Overall morbidity	Non-surgical complications	Surgical complications	Mortality	Ileus	Re-hospitalization
ER *vs.* Trad.	30 *vs.* 39.4%	13.4 vs 19.9%	17 *vs.* 19.1%	0.9 *vs.* 0.8%	-	4.4 vs 4.8%
Size of the effect	-39%	-42%	-10%	0%	-1 day after ER	-7%
p-value	0.0003	0.0001	0.41	0.55	0,00001	0.77
I^2 *	65%	15%	4%	0%	98%	0%

Table 1: Results of the meta-analysis by Zhuang CL *et al.* for colorectal surgery [6]

- Trad.: traditional
- I^2 : heterogeneity test for the different studies : the lower the I^2 , the more the studies are homogeneous

Table 2: Results of the meta-analysis by Deng QF *et al.* for orthopedic surgery [9]

	Overall morbidity	Mortality	Transfusions	Re-hospitalization
RR: [95% CI]	0.74 [0.62-0.87]	0.48 [0.27-0.85]	0.43 [0.37-0.51]	0.86 [0.56-1.30]
Size of the effect	-26%	-52%	-57%	/
p-value	0.0004	0.01	0.0001	0.46
I^2 *	0%	10%	28%	55%

- RR: Relative Risk

- 95%CI : 95% Confidence Interval
- I^2: heterogeneity test for the different studies : the lower the I^2 , the more the studies are homogeneous
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Table 3: Generic pre- and intra-operative elements of the ER protocol that may influence post-operative morbidity and mortality

Pre-operative
Management of co-morbidities
Correction of anemia
Management of malnutrition
Smoking cessation
Intra-operative
Prevention of hypothermia
Obtimal vascular volume replacement
Multimodal morphine-sparing anesthesia
Corticosteroids
Minimally-invasive surgery
Strategies to minimize blood loss
Systematic avoidance of nasogastric tubes
Thromboprophylaxis