



Marginal gain, does it matter?

Lorenzo Rosner¹, Michel Gonzalez²

¹Service of Anesthesiology, ²Service of Thoracic Surgery, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Correspondence to: Michel Gonzalez, MD. Division of Thoracic Surgery, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Email: Michel.Gonzalez@chuv.ch.

Provenance: This is an invited article commissioned by the Section Editor Laura Chiara Guglielmetti (Cantonal Hospital Winterthur, Kantonsspital Winterthur, Switzerland).

Comment on: Bjerregaard LS, Jensen PF, Bigler DR, *et al.* High-dose methylprednisolone in video-assisted thoracoscopic surgery lobectomy: a randomized controlled trial. *Eur J Cardiothorac Surg* 2018;53:209-15.

Submitted Apr 02, 2019. Accepted for publication Apr 09, 2019.

doi: 10.21037/jtd.2019.04.52

View this article at: <http://dx.doi.org/10.21037/jtd.2019.04.52>

In the field of thoracic surgery, there is now sustained enthusiasm about pre- and perioperative management of lung resection to improve post-operative outcome. Enhanced recovery after surgery (ERAS) is a multimodal approach that combines various procedures identified as relevant in the medical literature to optimize the recovery of the patient. These procedures are known to have a modest benefit when taken alone, but may have a more than additive effect when put together.

The concept behind such programs of accelerated recovery is that of marginal gains and it is well described in various sports. The idea is to identify individual elements during the management that are optimized separately to improve the post-operative outcome of the patient. In this sense, the ERAS procedure seems attractive since the international ESTS/ERAS guidelines have just been published establishing some recommendations for the management of thoracic surgical patients (1). ERAS is now being assessed and implemented in thoracic surgery and has already resulted in decreased post-operative complications, shortened length of stay and decreased costs (2-6).

One of the main, ongoing problem in thoracic surgery is pain management. A standardized multimodal approach is recommended to control pain with aim to decrease post-operative complications and facilitate early ambulation. During video-assisted thoracic surgery (VATS), regional anesthesia may be managed by intercostal blockage or catheter with continuous perfusion of local anesthesia to reduce opioid use. In addition, oral medication with acetaminophen or paracetamol and non-steroidal anti-

inflammatory drugs (NSAIDs) is regularly administrated to all patients. Glucocorticoid (GC) may also be administrated to reduce pain (1). Yet, some VATS procedures are still associated with non-negligible post-operative pain, warranting ongoing research to address this issue. In addition, it cannot be stated that a gold standard exists on the optimal pain management for VATS procedures, in the sense that it exists for thoracotomies (7). It is indeed possible that the specifics of VATS will require differential pain management procedures altogether, which have yet to be identified.

Well-known clinical effects of GCs include analgesic, antiemetic, antipyretic and anti-inflammatory properties (8,9). The most commonly used GCs are prednisolone, methyl-prednisolone (MP) and dexamethasone. The anti-inflammatory potency of prednisolone, MP and dexamethasone is 4, 5 and 25 times more important than cortisol, respectively (8). Perioperative administration of a single dose of GC has been routine practice for decades in elective surgery for various surgical specialties. The properties of dexamethasone or MP may modulate the inflammatory response to surgical stress with possible implications for post-operative recovery. More specifically, it has been reported that a single dose of GC has convincing anti-inflammatory effects in many major surgical procedures, provided it is administered with adequate timing (1-2 hours before the start of the procedure) (8).

Biologically, GCs block both the cyclooxygenase and lipo-oxygenase pathways in the inflammatory cascade, with a profound effect in the eicosanoid and the prostanoid

pain mediation. Their administration has been shown to decrease blood levels of pro-inflammatory mediators such as interleukin (IL)-6, IL-8, α -tumor necrosis factor (TNF) or C-reactive protein (CRP). These findings were mostly reported in cardiac surgery during cardio-pulmonary bypass (CPB) procedures, where inflammatory response is higher than in other surgical procedures (10). In thoracic surgery, one randomized study failed to demonstrate a major effect of GC administration on pro-inflammatory cytokines (11). However, another study showed that complement activation was inhibited by the administration of a high dose of MP (12). The administration of GCs has been associated with a modest benefit on post-operative pulmonary function assessed by spirometry after CPB, abdominal or lung surgery, although the mechanism is not clearly understood (8,13).

The administration of GCs has been reported to be effective alone or with other antiemetics for prevention of post-operative nausea and vomiting (PONV) through multiple targets: exerting a central antiemetic effect via the inhibition of prostaglandin synthesis and release of endogenous opioids, via a direct action at the solitary tract nucleus and via interaction with the neurotransmitter serotonin (14). The appearance of PONV is a major problem in surgery, which impacts the quality of early recovery and represents the leading cause of patient dissatisfaction in the immediate post-operative period. A meta-analysis including eight randomized clinical trials (RCT) showed that a single dose of dexamethasone significantly reduces PONV when compared to a dose of placebo in various surgical procedures (14). Recently, a single 8-mg dose of dexamethasone administered before visceral surgery has been shown to reduce PONV for the first 24 h and antiemetic needs for up to 72 h post-surgery (15).

The effect of GC administration on pain is not completely understood but seems correlated to a decrease of tissue bradykinin levels, a release of neuropeptides from nerve endings, a reduction of prostaglandin synthesis as well as a direct inhibitory effect on signal transmission in nociceptive C-fibers (16,17). In thoracic surgery, the administration of a high GC dose was significantly associated (compared to placebo) with decreased pain 4 hours after thoracotomy and on day 1 during rest as well as 4 and 8 hours after thoracotomy and on day 2 during cough (13). The long-term immune-suppressive and oncological effects of steroid-based antiemetic drugs are not known. The risks associated with GC administration include gastric irritation, impaired wound healing, impaired glucose homeostasis and sodium retention. The likelihood of these adverse effects does not seem to be

significantly increased after a single dose administration (18). The optimal dose that balances the advantages against these and other risks has yet to be defined.

In their recent double-blind randomized controlled trial, Bjerregaard *et al.* investigated the effect of high dose MP administration (125 mg) for analgesia in VATS lobectomy (19). Their study was conducted in a well-regarded center experienced in VATS procedure with standardized perioperative management. The MP or placebo was given blindly to patients in the context of a standardized multimodal analgesia. All patients received a paravertebral nerve block and an intercostal catheter with infusion of morphine and bupivacaine. Additional oral medication included paracetamol, NSAIDs and Gabapentin. The MP was administrated after induction of anesthesia, but before the start of the procedure. Ninety-six patients were included in the study and groups were not perfectly matched in term of gender and ASA score, although other elements showed an acceptable balance between both groups. The MP group presented significantly decreased median pain score on the day of surgery at rest [numeric rating scale (NRS) 1.6 *vs.* 2.0, $P=0.019$] and after mobilization to a sitting position (NRS 1.7 *vs.* 2.5, $P=0.004$). Pain score was not significantly different during arm abduction or coughing. In addition, PONV and fatigue were significantly reduced on the day of surgery, but the effect was not prolonged to post-operative day 1 or 2. Complications possibly related to MP administration, such as wound infection, were not more frequent after MP administration (10% *vs.* 17%, $P=0.15$) but the authors did observe a sub-clinical, transient elevation of blood glucose levels on the day of surgery in some patients who received MP. Six non-diabetic patients required insulin administration due to this increased blood glucose level, but none of them presented clinical symptoms.

In our opinion, this study illustrates very well the concept of marginal gains in the context of an ERAS program. Although the clinical relevance of administering a single pre-operative dose of MP seems moderate, the investigators demonstrate better pain control on the day of surgery and decreased PONV and fatigue without increased risk of infections or impaired wound healing. The authors point out that the modest effect of MP on pain was probably attenuated by their optimal multimodal pain management with intercostal catheter and paravertebral nerve block. It is also possible that the exact gain of GC administration might depend on its timing (no later than 1–2 hours before surgery, to allow onset of its anti-inflammatory effect in time for the

start of the procedure). Yet, neither comment should not obliterate the fact that modest as it may be, the decrease in post-operative pain is real. This is in good agreement with various studies showing that numerous aspects of the stress responses to surgery, organ dysfunctions, and postoperative recovery can be improved by administering a pharmacologic dose of GC before surgery.

Pre-operative GC administration has showed to improve pain, PONV and fatigue. These elements are relevant in the context of an enhanced recovery program since they improve the patient's wellbeing and help early ambulation, thereby indirectly decreasing the rate of post-operative complications. In this sense, the phrase "marginal gain" seems appropriate for the pre-operative use of a single GC dose, with a clear emphasis on both words.

Acknowledgements

We would like to thank Matthieu Zellweger for editorial help on the manuscript.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS(R)) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg* 2019;55:91-115.
2. Gonzalez M, Abdelnour-Berchtold E, Perentes JY, et al. An enhanced recovery after surgery program for video-assisted thoracoscopic surgery anatomical lung resections is cost-effective. *J Thorac Dis* 2018;10:5879-88.
3. Brunelli A, Thomas C, Dinesh P, et al. Enhanced recovery pathway versus standard care in patients undergoing video-assisted thoracoscopic lobectomy. *J Thorac Cardiovasc Surg* 2017;154:2084-90.
4. Madani A, Fiore JF Jr, Wang Y, et al. An enhanced recovery pathway reduces duration of stay and complications after open pulmonary lobectomy. *Surgery* 2015;158:899-908; discussion 908-10.
5. Rogers LJ, Bleetman D, Messenger DE, et al. The impact of enhanced recovery after surgery (ERAS) protocol compliance on morbidity from resection for primary lung cancer. *J Thorac Cardiovasc Surg* 2018;155:1843-52.
6. Van Haren RM, Mehran RJ, Mena GE, et al. Enhanced Recovery Decreases Pulmonary and Cardiac Complications After Thoracotomy for Lung Cancer. *Ann Thorac Surg* 2018;106:272-9.
7. Steinhorsdottir KJ, Wildgaard L, Hansen HJ, et al. Regional analgesia for video-assisted thoracic surgery: a systematic review. *Eur J Cardiothorac Surg* 2014;45:959-66.
8. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. *J Am Coll Surg* 2002;195:694-712.
9. Sauerland S, Nagelschmidt M, Mallmann P, et al. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. *Drug Saf* 2000;23:449-61.
10. Hall RI, Smith MS, Rocker G. The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological considerations. *Anesth Analg* 1997;85:766-82.
11. Tønnesen E, Wanscher M, Hohndorf K, et al. Effect of methylprednisolone on the cytokine response in patients undergoing lung surgery. *Acta Anaesthesiol Scand* 1993;37:410-4.
12. Mikawa K, Ikegaki J, Maekawa N, et al. Perioperative effect of methylprednisolone given during lung surgery on plasma concentrations of C3a and C5a. *Scand J Thorac Cardiovasc Surg* 1990;24:229-33.
13. Bigler D, Jonsson T, Olsen J, et al. The effect of preoperative methylprednisolone on pulmonary function and pain after lung operations. *J Thorac Cardiovasc Surg* 1996;112:142-5.
14. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2000;90:186-94.
15. DREAMS Trial Collaborators and West Midlands Research Collaborative. Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). *BMJ* 2017;357:j1455.
16. Hargreaves KM, Costello A. Glucocorticoids suppress levels of immunoreactive bradykinin in inflamed tissue as evaluated by microdialysis probes. *Clin Pharmacol Ther* 1990;48:168-78.
17. Hong D, Byers MR, Oswald RJ. Dexamethasone treatment reduces sensory neuropeptides and nerve sprouting reactions in injured teeth. *Pain* 1993;55:171-81.

18. Toner AJ, Ganeshanathan V, Chan MT, et al. Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery: A Systematic Review and Meta-analysis. *Anesthesiology* 2017;126:234-48.
19. Bjerregaard LS, Jensen PF, Bigler DR, et al. High-dose methylprednisolone in video-assisted thoracoscopic surgery lobectomy: a randomized controlled trial. *Eur J Cardiothorac Surg* 2018;53:209-15.

Cite this article as: Rosner L, Gonzalez M. Marginal gain, does it matter? *J Thorac Dis* 2019;11(Suppl 9):S1313-S1316. doi: 10.21037/jtd.2019.04.52