

FAST TRACK SURGERY: CURRENT CONCEPTS

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Abstract: The concept of fast track surgery, which could be expressed as multimodal control of perioperative pathophysiology, seems to be a highly promising approach to improve surgical outcome. The principles and techniques embodied in this approach will eventually be integrated into the care of all surgical patients. To achieve this goal resources should be allocated for evaluation and documentation of the effects of fast track surgery and related systems on cost, postoperative morbidity, safety, and overall patient well being. Many multicenter trials are needed to effectively establish the yet unproven superiority of fast track surgery in long-term surgical outcomes. Fast track module based upon peri-operative optimization can be a meaningful step in improving both the outcomes as well as optimal utilization of constrained health resources.

INTRODUCTION

Surgery is undergoing revolutionary changes due to newer approaches to pain control, the introduction of techniques that reduce the perioperative stress response, and the use of minimally invasive operations. Subsequently, many surgical procedures (such as arthroscopic surgery, laparoscopic cholecystectomy, eye surgery, sterilisation procedures, herniorrhaphy, and cosmetic operations) are routinely performed on an outpatient basis. Recently published pilot studies suggest that when these newer approaches are used in patients undergoing more complex elective surgical procedures, postoperative complications can be reduced, length of hospital stay decreased, and time to recovery shortened. This review of recent advances made in this newly developing specialty of fast track surgery will emphasise techniques that facilitate early recovery after major surgical procedures.

WHAT IS FAST TRACK SURGERY?

Fast track surgery combines various techniques used in the care of patients undergoing elective operations. The methods used include epidural or regional anaesthesia, minimally invasive techniques, optimal pain control, aggressive postoperative rehabilitation, early enteral (oral) nutrition and ambulation. The combination of these approaches reduces the stress response and organ dysfunction and therefore greatly shortens the time required for full recovery.

Recent advances in understanding perioperative pathophysiology have indicated that multiple factors contribute to postoperative morbidity, length of stay in hospital, and convalescence. Major improvements in surgical outcome may therefore require multifaceted interventions. Ambulatory surgery has become routine for many procedures with a well documented record for safety and low morbidity, even in patients at high risk.

Studies have evaluated somewhat similar approaches toward larger operations which carry more risk. Preliminary results from predominantly non-randomised trials have been positive. These studies have included high risk elderly patients undergoing operations such as segmental colonic resection, prostatectomy, and aortic aneurysmectomy. These preliminary data indicate topics for further randomised trials; the data need to be confirmed and

extended to include end points of reduced costs, preserved safety, and patient satisfaction.

The preliminary results for fast track surgery have been encouraging. Abdominal procedures like Inguinal hernia repair¹, Cholecystectomy (laparoscopic² mini-incision), Fundoplication, Open and laparoscopic³ colorectal procedures, Complex pelvic-colorectal procedures, Rectal prolapse, Pancreaticoduodenectomy, complex biliary tract procedures have all shown reduced hospital stay, early mobility and return to work and decreased morbidity emphasizing the importance of adopting principles of fast track surgery. Similar results were obtained for other procedures like Mastectomy⁴, vascular procedures, various urologic procedures, Neurosurgery and gynecologic surgeries.

PREOPERATIVE EVALUATION AND EDUCATION

The aims preoperatively should be

1. Optimize organ functions for patients with cardiac disease, chronic obstructive lung disease, diabetes mellitus, and other disorders, according to current recommendations.
2. Promote abstinence and other pharmacologic means to stop substance abuse in chronic alcoholics^[5] and smokers.
3. Education of patients about perioperative care before the operation reduces the need for pain relief, can include instruction on relaxation techniques which can be used after the operation, reduces anxiety, and improves outcome.

OPTIMISING ANAESTHESIA

Recent developments in techniques in anaesthesia have optimised conditions for surgeons to operate while allowing for very early recovery of vital organ function after major procedures. Thus, the introduction of rapid short acting volatile anaesthetics (for example, desflurane and sevoflurane), opioids (for example, remifentanyl), and muscle relaxants have facilitated expansion of ambulatory surgery for minor to moderate procedures. The use of anaesthetic techniques that provide for minimal carryover of opioid effects into the recovery period, supported by other non-opioid analgesic methods, may minimise postoperative complications and facilitate recovery after major procedures. Neural blockade techniques have been developed in recent years to provide attenuation of the surgical stress response, thereby reducing postoperative organ dysfunction and allowing early recovery⁶. Regional anaesthetic techniques that use local anaesthetics can reduce the classic

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pituitary, adrenocortical, and sympathetic responses to surgery⁶. Neurogenic blockade (either by administering a local anaesthetic in the spinal or epidural space or by using local anaesthetic techniques that block the nerve impulses from an area) improves postoperative nitrogen economy and glucose intolerance but does not modify inflammatory or immunological responses. Relevant to clinical care, continuous neural blockade for 24 to 48 hours is necessary for a pronounced reduction in perioperative stress in major surgery. Moreover, the systemic effects of local or regional anaesthesia/analgesia or, the stress response are greatest in procedures on the lower body (lower extremities or pelvis) compared with upper abdominal and thoracic operations. The effects of regional anaesthetic techniques are manifest by improved pulmonary function, decreased cardiovascular demands, reduced ileus, and improved pain relief⁶. A recent meta-analysis of regional anaesthetic studies showed a 30% reduction in morbidity compared with general anaesthesia⁶.

OPERATIVE TECHNIQUES

Minimal invasive surgery

The use of minimal invasive abdominal surgical techniques, such as laparoscopic cholecystectomy, has not reduced the early endocrine mediated metabolic response to surgery, but this approach has been associated with a decrease in various inflammatory responses and immunodysfunctions. Pulmonary function seems to be improved and postoperative ileus reduced with minimal invasive approaches.

Intraoperative normothermia

Operating rooms are cold. Patients are inadequately clothed and receive anaesthetics which hamper their homeostatic defenses to cold. As a result, patients undergoing operations lasting over two hours often become hypothermic, with a fall of core temperature of 2-4 [degrees] C. During rewarming cortisol and catecholamines are released, which augment the stress response of the operation⁷. Keeping patients warm has been associated with a threefold decrease in the rate of wound infection, a reduction in operative blood loss, a decrease in untoward cardiac events, including ventricular tachycardia, and a reduction in nitrogen excretion and patient discomfort⁷. Maintenance of a normal temperature during surgery is central to reducing the stress of the surgical procedure and reducing the risk of organ dysfunction.

POSTOPERATIVE CARE

For the first 24 hours bed rest is undesirable as it increases muscle loss and weakness, impairs pulmonary function, and predisposes to venous stasis and thromboembolism. Nasogastric tubes and drain placements have not shown benefit. Oral intake is commonly limited in the postoperative period. Presently there are no available clinically effective drugs that enhance gastric emptying, and with the attenuation of ileus associated with epidural anaesthesia, oral intake can often be successfully initiated six hours after surgery, even after colonic operations which use an anastomosis. Postoperative pain should be vigorously treated as it may amplify the surgical stress responses and organ dysfunction and prolong recovery. After minor to moderate operations patients should receive non-opioid analgesics, such as non-steroidal anti-inflammatory agents, to avoid side effects related to use of opioid drugs, which prolong recovery. Major surgical procedures with high intensity pain and subsequent organ dysfunction induced by stress require the use of invasive analgesic methods, such as

continuous epidural analgesia, to hasten recovery. Optimal management of acute pain after major procedures is a prerequisite for fast track surgery and should be used for all surgical patients. ***Nausea, vomiting, and ileus*** The ability to resume a normal diet is essential for a successful fast track surgical programme after both minor and major procedures. Principles for rational prophylaxis and treatment of nausea and vomiting have been developed, and several agents including droperidol, antiserotonergic drugs, and analgesic regimens with reduced use of opioid drugs will reduce these symptoms. The use of multifaceted regimens for nausea and vomiting in combination with dexamethasone requires further evaluation. Postoperative ileus, which is predominantly caused by a combination of inhibitory neural sympathetic visceral reflexes and the intestinal inflammatory response, may be considerably alleviated by a combination of epidural local anaesthetics, analgesia with reduced use of opioid drugs, minimally invasive surgery, and pharmacotherapy⁸. Preliminary studies show that such regimens, when combined with early enteral nutrition, may almost completely prevent paralytic ileus after colonic resection.

The second to fifth postoperative day

Recovery from an operation depends on several factors, including the resolution of pain and fatigue. Fatigue in the early post operative period is related to altered sleep within the hospital setting because of noise, environmental disturbances, drugs, and possibly inflammatory factors. Loss of muscle strength and loss of weight because of reduced food intake have been related to fatigue, which occurs after a week or so. Reduction of surgical stress, early enteral nutrition, and mobilisation are therefore important interventions which counteract fatigue and aid recovery.

FUTURE DEVELOPMENTS AND CONCERNS

The initial promising results from the fast track surgical programs studied suggest that such programs can achieve major care improvements in terms of reducing postoperative stay. At present, however, sufficient scientific documentation is lacking for many commonly performed major operations. Thus, there is a need for additional data, in particular, data on the potential positive effects of fast track surgery on postoperative morbidity. The necessary data would probably be best obtained through multicenter trials using identical protocols⁹.

As yet, it has not been conclusively demonstrated that reducing the duration of hospitalization necessarily reduces morbidity, though data from studies addressing colonic and vascular procedures suggest that nonsurgical (i.e., cardiopulmonary and thromboembolic) morbidity may be reduced and overall postoperative recovery (assessed in terms of exercise performance and muscle power) enhanced. More study is required in this area. Future trials should also focus on identifying any factors that might be limiting even more aggressive early recovery efforts, so that more effective fast track programs can be designed. Finally, studies are needed to identify potential high-risk patient groups for whom fast track surgery may not be appropriate or who may need to be hospitalized for slightly longer periods to optimize organ function.

All of the studies on the economic implications of fast track surgical programs and critical pathways have documented substantial cost savings. It should, however, be borne in mind that the last portion of a hospital stay is much less expensive than the initial portion; thus, the cost savings in this area may turn out to be smaller than

they would at first appear¹⁰⁻¹². This should not hinder development of ways and means in fast track surgery because a reduction in morbidity and early return to work adds to cost benefits.

The basic concept of fast track surgery, which could be expressed as multimodal control of perioperative pathophysiology, seems to be a highly promising approach to improving surgical outcome. The principles and techniques embodied in this approach should eventually be integrated into the care of all surgical patients as they lead to shorter hospital stay, early return to work and less postoperative pain and morbidity for most, if not all, surgical procedures.

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Drug Profile

Darusentan : A promising drug for resistant hypertension

Introduction: Resistant hypertension is defined as inability to reduce blood pressure to less than 14/90 mm Hg using an adequate and appropriate triple-drug regimen, including an oral diuretic, with all three drugs near the maximum recommended dose¹ about 10% to 30% of hypertension patient for the remain of developing cardiovascular and renal complications.

Mechanism of Action: Endothelin (ET) is a small peptide hormone that is believed to play a critical role in the control of blood flow and cell growth. Elevated endothelin blood levels are associated with several cardiovascular disease conditions, including pulmonary arterial hypertension (PAH), chronic kidney disease, hypertension, acute myocardial infarction, chronic heart failure and stroke². Endothelin 1 (ET-1), which consists of 21 amino acid residues is the predominant isoform of the endothelin peptide family, which also includes ET-2 and ET-3³. It exerts various biological effects, including vasoconstriction and the stimulation of cell proliferation in tissues both within and outside cardiovascular system. ET receptors have been divided into two different subtypes, ETa (ET-1 selective) and ETb (nonselective for the isopeptides)⁴. ETA receptors are distributed predominantly in vascular smooth muscle, cardiac myocytes and intestine, whereas ETB receptors are found on endothelial cells, cerebral cortex, kidney and trachea. The binding of endothelin to ETA receptors located on smooth muscle cells causes vasoconstriction. However, the binding of endothelin to ETB receptors located on the vascular endothelium causes vasodilation through the production of nitric oxide and prostacyclin. In addition, ETB receptors in the lung are a major pathway for the clearance of ET-1 from plasma⁵. The activity of the ETB receptor is thought to be counter-regulatory, protecting against excessive vasoconstriction. Hence, selective ETA receptor antagonists can counteract negative effects of endothelin by preventing vasoconstriction and cell proliferation, while preserving the beneficial effects mediated through ETB receptor (Blocking the Beast while Leaving the Beauty Untouched) Dr. experimental stands the drug has shown benefit in lung to oxide. Darusentan is a member of a class of therapeutic agents known as endothelin receptor antagonists (ERA) that is selective for the ETA receptor and is being developed as an oral therapy for the treatment of uncontrolled hypertension based on the evidence that it significantly reduces both systolic and diastolic blood pressure in patients who have failed to achieve optimal blood pressure even with multiple drugs.

Darusentan acts through a different mechanism than existing anti-hypertensive therapies. It is an ERA that is selective for the ETA receptor and can block the negative effects of endothelin by preventing vasoconstriction and cell proliferation, while preserving the beneficial effects associated with ETB receptor stimulation.

Pharmacokinetic parameters: the affinity of darusentan for ETA receptors is about 130 times than that for ETB receptors. The compound demonstrates high potency, high oral bioavailability and has a long half-life (16-18 hrs) that is suitable for once daily dosing⁵. In addition, the compound does not induce or inhibit the Cytochrome P450 metabolic pathway.

Adverse effects: Darusentan is well tolerated and exhibits favorable safety profile. In the trials with darusentan, headache was the most commonly reported adverse event, with no relevant difference among placebo and active treatment groups. Other frequent adverse events include flushing and peripheral edema were dose-dependent. Whereas, previous clinical trials with other ERAs in patients with hypertension demonstrated dose-related hepatotoxicity requiring withdrawal of therapy for safety reasons, there were no treatment-related elevations in liver enzymes with darusentan. **Clinical Trials:** Earlier studies with darusentan in patients with Chronic heart failure did not show significant improvement in clinical outcome⁶. Subsequently, trials in patients with uncontrolled hypertension or resistant hypertension were undertaken.

Preclinical trial : In a rat model of genetic hypertension, animals from the salt-sensitive (SBH/y) and salt-resistant strains (SBN/y) were either salt-loaded with deoxycorticosterone acetate (DOCA) and salt or fed a normal diet. Salt-loading in SBH/y increased systolic blood pressure by 75 mm Hg and urinary albumin excretion 23-fold (P<0.0001). However when darusentan was administered in additional salt-loaded groups it attenuated the rise of systolic blood pressure (50%) and urinary albumin excretion (63%, P<0.01, respectively)⁷. Clinical Trials: In 2000, Hy-

pertension Endothelin Antagonist Treatment (HEAT) study which was a randomized, double-blind, placebo-controlled, dose-ranging trial evaluated the safety and efficacy of darusentan in 392 patients with moderate essential hypertension (Stage-II). The result of this study demonstrated that darusentan produced statistically significant reductions in diastolic and systolic blood pressures in a dose-dependent manner and was well tolerated⁵. In July 2004, a Phase 2b randomized, double-blind, placebo-controlled clinical trial was undertaken to evaluate the safety and efficacy of darusentan in patients with resistant hypertension, patients with systolic blood pressure greater than or equal to 140 mmHg despite treatment with full doses of three anti-hypertensive medications, one of which was a diuretic were enrolled in the study. A total of 115 patients were randomized to darusentan or placebo at approximately 30 investigative sites in the United States. Patients underwent forced titration every two weeks through 10,50,100 and 150 mg of darusentan or placebo until the target dose of 300 mg once daily was achieved. The treatment period was ten weeks followed by a two week drug withdrawal period. The trial results demonstrated that 300 mg of darusentan dosed once daily provided statistically significant, placebo-corrected reductions of 11.6 mmHg in systolic blood pressure and 5.8 mmHg in diastolic blood pressure. Based on encouraging results of Phase 2 trials, company has initiated Phase 3 clinical trial in June 2006 and is presently recruiting patients for this trial. This trial is entitled DORADO – Fixed Doses of Darusentan as Compared to Placebo in Resistant hypertension. It is a randomized, double-blind, placebo-controlled, multi center, parallel group study to evaluate the efficacy and safety of fixed doses of darusentan subjects with resistant systolic hypertension receiving combination therapy with four or more antihypertensive drugs, including a diuretic. Indication & dosage: Darusentan is indicated in resistant hypertension and has shown efficacy at dose of 300mg daily Through trials with darusentan were undertaken as potential therapy for congestive heart failure receptor blockers which have an associated risk of hepatotoxicity, darusentan is well tolerated with no such risk. Conclusion: ET antagonists are promising new agents in the treatment of cardiovascular diseases. Darusentan could be the first of a new class of agents for treating resistant hypertension. Although it is primarily being investigated as antihypertensive drug but various preclinical studies with darusentan in experimental models of acute lung injury have also shown promising results comparable to inhaled Nitric oxide (iNO) by improving gas exchange and preventing an increase in mean pulmonary artery pressure⁸. More information about darusentan is available on websites

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