Efficacy of pre-extubation intravenous administration of fentanyl on hemodynamic stabilization in adult controlled hypertensive patients receiving chemotherapy for breast cancer before mastectomy operation. A prospective randomized controlled study

Presented by

Ahmed Salman Solyman Salman

MB.BCH

Submitted for partial fulfillment of
Master Degree in Anaesthesiology

Supervised by

Professor Dr. Amel Abo Elela

Professor of anaesthesiology ,ICU and pain management
Faculty of medicine
Cairo University

Professor Dr. Sahar Abdelhalim Mohamed

Professor of anaesthesiology ,ICU and pain management
National cancer institute
Cairo University

Dr. Ashraf Mohammed Abderahem

Lecturer of anaesthesiology ,ICU and pain management
Faculty of medicine
Cairo University

Faculty of medicine
Cairo University
2015

Keywords: Preextubation, Fentanyl, Heamodynamics, time of extubation**.**

Abstract: in patients with controlled hypertension, received chemotherapy underwent mastectomy operation for breast cancer; fentanyl 1mic/kg i.v. given at the time of closure of anesthesia is a simple, effective, and practical method in blunting cardiovascular responses to tracheal extubation and emergence from anesthesia. further studies are required in patients with CAD and cerebrovascular disease in order to evaluate the advantage, beneficial effects, and safety of fentanyl compared with these factors in other drugs used to attenuate the hemodynamic changes caused by extubation.This does not lead to respiratory depression or prolonged recovery. The use of 2 mic/kg fentanyl at the same time provide much more control of the heart rate than 1mic/kg which maybe beneficial for the patients with coronary artery disease (CAD) but with some delay in the extubation time in comparison to 1mic/kg of fentanyl.

Acknowledgement

Firstly, I thank God for helping me in the completion of this work and ask him to bless it .

Special thanks, greatful and love to Dr ***Salman*** *and Mrs* ***Fatma*** *my parents for every thing.*

I would like to express my deepest appreciation and gratitude to Prof. Dr. ***Amel Aboelela*** *,Professor of anaesthesiology and Pain Therapy, faculty of medicine, Cairo University, for her honest supervision, guidance, and advice which have been of great help in the performance of this work. It was a great honor to work under her supervision.*

The words fail to express my gratefulness to Prof. Dr. ***Sahar Abdelhalim*** *, Professor of anaesthesiology and Pain Therapy, National Cancer Institute, Cairo University for her faithful supervision, constructive guidance and real interest in the progress of this work.*

I would also like to thank lecturer Dr. ***Ashraf Mohammad Abdelrahem*** *, lecturer of anaesthesiology and Pain Therapy ,Faculty of medicine, Cairo University, for his kind help in achieving this work.*

Finally, I would like to thank my dear wife ***Reema****, my Brothers, my sisters and my beloved friends for the care and support they gave me, through the work.*

Ahmed Salman Solyman Salman

2015

CONTENT

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Both tracheal intubation and extubation are associated with potentially dangerous effects such as hypertension, tachycardia, myocardial ischemia, arrhythmias and increased intracranial and intra-abdominal pressure(1). These potentially serious side effects during tracheal intubation can be solved and managed effectively and rapidly by administration of inhalational or intravenous anesthesia(2). On contrary, during extubation, if hypertensive crises occurs especially in hypertensive patients, anesthesiologist, if aware by such problem, may have less weapons to manage it. These hypertensive crises should pay more attention in patients with malignant tumors (3), as malignancy itself may induce abnormality in the proliferative pathway leading to increase peripheral resistance, as well as arterial hypertension which is the most frequent adverse effect of most chemotherapeutic agents (angiogenesis inhibitors)(4).On a dose-dependent basis, these drugs can worsen pre-existing hypertension, or can cause de novo hypertension to develop through endothelial dysfunction(5).Hypertension can occur at any time during treatment. Acute complications include heart failure, proteinuria with renal thrombotic microangiopathy, intracerebral hemorrhage, and operative related hypertensive crisis (5). Thus it's very important to obtund the stress response of both intubation and extubation in cancer patients undergoing surgery with paying more attention to extubation hypertensive crises, especially in patients under chemotherapy.

Fentanyl, a short acting opiate, has been used to attenuate stress response of both intubation and extubation. The peak respiratory depressant effect of a single intravenous dose of fentanyl citrate is noted 5 to 15 minutes following injection(6).Several doses of fentanyl (0.5, 1, 2, 2.5mcg/kg) were used to obtund the stress during induction of anesthesia (7). Also, fentanyl has been used to smoothen emergence from general anesthesia after surgery (8). However, its use at the end of the surgery in adult cancer patient is still not fully studied.

AIM OF THE WORK

The aim of the present work is to evaluate the benefits versus side effects of preextubation administration of fentanyl on hemodynamic stabilization versus delayed recovery. Two different doses of fentanyl were administered on adult controlled hypertensive female patients receiving preoperative chemotherapy scaduled for mastectomy operation.

CHAPTER (1)

CHEMOTHYRAPY AND HEAMODYNAMICS

The landscape of early breast cancer has changed dramatically with significant advancements in early screening and diagnosis and curative-intent therapies. Indeed, breast cancer–specific survival has improved by 20% during the past 30 years, and 5-year survival is now 98% for early-stage disease(9).As a consequence, the risk and nature of adjuvant therapy–induced immediate and late-occurring cardiovascular injury have similarly evolved. In women with early breast cancer cardiovascular disease (CVD) is now the predominant cause of mortality as indicated by Surveillance, Epidemiology, and End Results (SEER)–Medicare linked data(10).Additionally, these women are also at increased risk of Cardiovascular (CVS) disease compared with age-matched women without a history of breast cancer(11).

Significant cardiac safety concerns about anticancer therapy were first described by Von Hoff and colleagues(12), identifying dose-dependent and progressive left ventricular (LV) dysfunction manifesting as symptomatic heart failure in patients receiving anthracyclines. From this work and others(13), anthracycline-induced cardiovasculer toxicity(14) is now a well-recognized adverse side effect. More recently, randomized trials have demonstrated that human epidermal growth factor receptor 2 (HER2)–directed monoclonal antibodies (ie, trastuzumab) and newer multitargeted small-molecule inhibitors interfere with molecular pathways crucial to normal cardiac homeostasis(15),resulting in relatively high incidences of subclinical and overt cardiovascular toxicity.

Although cardiac toxicity with newer therapies has demonstrated reversibility, recovery of LV function after treatment cessation is uncertain at this time(16). Thus, to identify those individuals at high risk of cardiovascular toxicity, baseline measurement of LV ejection fraction (LVEF) is recommended by the American College of Cardiology (ACC) and American Heart Association (AHA) as standard of care for all breast cancer patients being considered for potentially cardiac-toxic treatment regimens(17).In addition, measurement of LVEF is Food and Drug Administration (FDA) mandated in all registrational breast cancer adjuvant trials involving an anthracycline- or a trastuzumab-containing regimen. Finally, use of endocrine therapy (eg, tamoxifen and aromatase inhibitors) in women with hormone receptor–positive breast cancer may also increase the risk of cardiovascular complications(19).

Despite the rapidly changing landscape of breast cancer management and the resultant changes in cardiovascular safety, several critical issues in the emerging field of "cardiovascular-oncology" remain unresolved. To ensure that this field keeps pace, a full understanding of the incidence, magnitude, and consequences of cardiovascular side effects of adjuvant therapy is an essential first step in optimizing early breast cancer management. Against this background, the purpose is to comprehensively review several pivotal unaddressed issues concerning the definition, incidence, detection, and clinical importance of cardiovascular toxicity in early breast cancer(20).

Chemotherapeutic agents do not specifically target tumorcells, but rather interfere with cell division or inhibit enzymes involved DNA replication or metabolism. These drugs therefore also damage the normal dividing cells of rapidly regenerating tissues, such as those of the bone marrow, gut mucosa and hair follicles. Cancer chemotherapy is limited by a lack of specificity, resulting in damage to not only cancer cells but also normal

cells. This creates a narrow therapeutic index. Considering the side effects associated with traditional chemotherapies and the possibility of interrupting a tumor's supply of oxygen and nutrient, there has been great interest taken in the targeting of tumor vasculature and much effort has been directed towards the development of anti-angiogenic agents that could disrupt this angiogenesis. Administration of the maximum tolerated dose (MTD2) is uasually associated with maximum clinical benefit(21). Toxicities may be caused or depend on the duration of the treatment and different rates of antiangiogenic onset. Bevacizumab has been associated with gastrointestinal perforations and wound-healing complications and found to possibly cause acute life-threatening problems (22). Meanwhile, anthracycline chemotherapy may reduce the left ventricular ejection fraction (LVEF), which can also ultimately be life threatening (23). The inhibitors might induce a reciprocal increase in expression of the growth factor or its receptor (i.e., VEGF or VEGFR) and provoke toxicity of these agents.

Underlying Mechanisms of Cardiovascular Events

Anthracyclines

Suggested mechanisms of anticancer effects include intercalation into DNA, preventing macromolecule synthesis; generation of reactive oxygen species, leading to DNA damage or lipid peroxidation; and topoisomerase II inhibition, inducing DNA damage and apoptosis(24).Anthracycline-induced generation of reactive oxygen species is a central mediator of numerous direct adverse myocardial consequences (Figure 1)(24). For instance, anthracyclines both accelerate myofilament apoptosis via activation of the tumor suppressor protein p53(25) and suppress sarcomere protein synthesis through depletion of

GATA-4–dependent gene expression(26) and cardiac progenitor cells(27). This imbalance between sarcomere synthesis and degradation results in impaired myocyte turnover, accumulation of senescent cells, and eventually the onset of myocardial dysfunction(28). Reactive oxygen species also stimulate cardiomyocyte calcium release and inhibit sarcoplasmic reticulum calcium reuptake, with the resulting cytosolic calcium overload leading to systolic (contractile) and diastolic (lusitropic) dysfunction(29).Anthracycline induction of inducible nitric oxide synthase and the generation of peroxynitrite, a reactive oxidant produced from the reaction of nitric oxide and superoxide anion, in the myocardium may trigger cell death and contribute to myocardial dysfunction(30). Finally, anthracyclines decrease AMP-activated protein kinase expression, triggering perturbations in mitochondrial substrate use and a decrease in ATP production(31).Collectively, these molecular mechanisms contribute to the pathogenesis of myocardial dysfunction and heart failure.

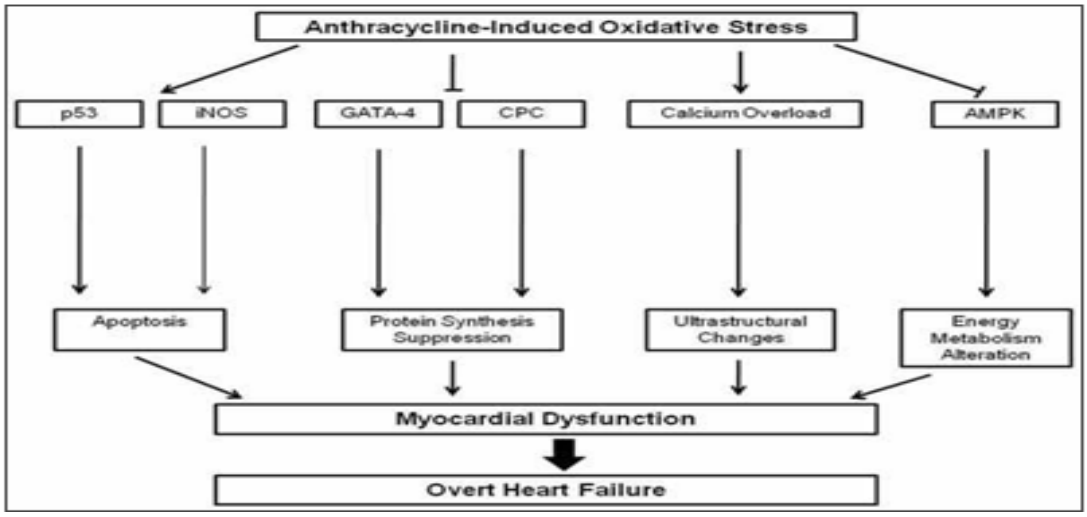

Figure 1 Mechanisms underlying anthracycline-induced cardiac toxicity. Anthracycline-induced generation of oxidative stress is a central mediator of accelerated myofilament apoptosis via upregulation of the p53 pathway and inducible nitric oxide synthase (iNOS), suppression of myofilament protein synthesis via inhibition of cardiac progenitor cells (CPCs) and GATA-4, calcium overload resulting in ultrastructural changes to myocytes, and alterations in cardiac energy metabolism via downregulation of AMP-activated protein kinase (AMPK). These changes lead to myocardial dysfunction and ultimately heart failure. Adapted from Scott et al(24).

Molecularly Targeted Therapeutics

Receptor tyrosine kinases are enzymes that act as critical mediators of normal cellular signal transduction and regulate diverse cellular processes, including cell cycle progression, metabolism, transcription, and apoptosis(32).Strategies for the prevention or interception of malignant-induced deregulated receptor tyrosine kinase signaling include the development of selective agents that target either the extracellular ligand-binding domain or the intracellular tyrosine kinase–binding region(34). HER2-directed therapies are receptor tyrosine kinase agents approved by the FDA for adjuvant treatment of early breast cancer that may have adverse myocardial consequences(35).

Of clinical importance, trastuzumab, the first FDA-approved anti-HER2 therapy, and pertuzumab, a newer agent undergoing phase II clinical trials, are associated with significant ventricular systolic dysfunction(36),whereas lapatinib may be associated with a lower incidence of decline in EF. In the normal heart, neuregulin-1β binds to HER (also known as ErbB) receptors on cardiomyocytes, leading to activation of the PI3K/Akt pathway promoting protein synthesis, cell survival, and protein hypertrophy and reducing protein degradation (Figure 2).Extracellular HER2-directed agents (ie, trastuzumab and pertuzumab) inhibit neuregulin-1β release(37),leading to a marked decrease in both total and phosphorylated Akt, thus limiting cardiomyocyte cell hypertrophy and survival and protein regulation(38).

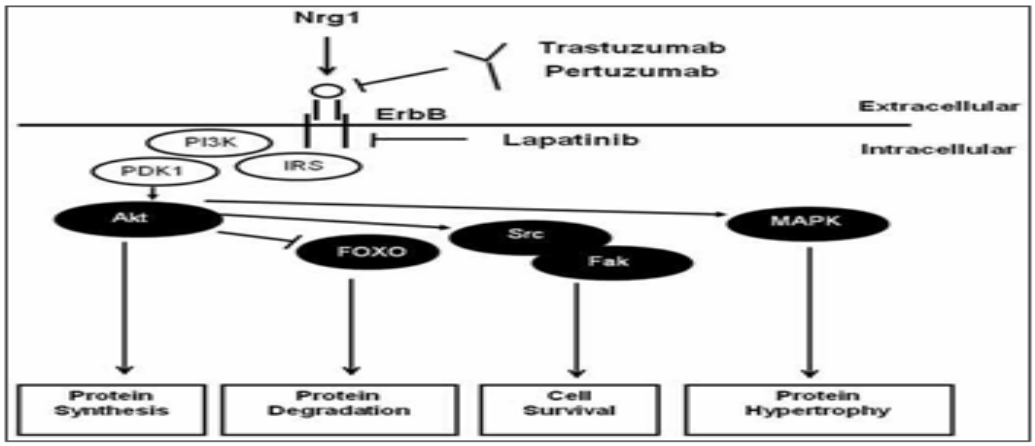

Figure 2 Mechanisms underlying molecularly targeted therapeutics-induced cardiac toxicity. Inhibition of neuregulin-1β (Nrg1)/ErbB receptors with human epidermal growth factor receptor 2 (HER2)–directed therapies affects numerous signaling pathways, resulting in suppression of myofilament protein synthesis via the PI3K-Akt pathway, suppression of protein hypertrophy via the mitogen-activated protein kinase (MAPK) pathway, suppression of cell survival via the Src/Fak pathway, and upregulation of protein degradation via FOXO signaling. Fak indicates focal adhesion kinase; NO, nitric oxide; and PI3K, phosphatidylinositol 3-kinase(38).

Endocrine Therapies

The underlying mechanisms of cardiovascular toxicity remain to be elucidated; however, a brief overview of the potential cardiovascular consequences of endocrine therapies is provided. Traditional endocrine therapy (tamoxifen, oophorectomy) for women with hormone receptor–positive breast cancer has not been clearly associated with cardiovascular injury. Although controversial, as a selective estrogen receptor antagonist/agonist, tamoxifen may have protective properties against myocardial infarction and ischemic heart disease related to a generally beneficial impact on serum lipids(39). However, these favorable benefits may be offset by a higher incidence of vascular events, particularly venous thromboembolism and stroke.The marked reduction in serum estrogen associated with the newer third generation of aromatase inhibitor therapy and the unfavorable changes in lipoprotein profiles raise concerns about the adverse cardiovascular effects of these agents. Compared with tamoxifen, aromatase inhibitor therapy has been associated with a slight increase in CVD events, although the incidence of thromboembolism was

significantly lower(40).No significant differences in the incidence of CVD events have been observed between aromatase inhibitor therapy and placebo. Long-term follow-up is required to fully assess the associated cardiovascular risks, if any, with aromatase inhibitor therapy.

Toxicities induced by anti-angiogenic therapy

Hypertension

VEGF activates the endothelial cells to stimulate the production of nitric oxide synthase, producing nitric oxide. Nitric oxide is used to relax the surrounding smooth muscle of blood vessels. Thrombosis is defined as a pathological formation of a thrombus or clot in a vessel and causes an obstruction to the flow of blood. The treatment of cancer patients with angiogenesis inhibitors has been associated with hypertension and a reduced LVEF (41). While the regulation of anti-hypertensive agents are quite effective in reducing the increase of blood pressure, bevacizumab- or anti-angiogenic TKI-induced hypertension might be lifethreatening and cause damage to the eyes, brain, kidneys and lungs.

Hypothyroidism and fatigue

The thyroid gland has many capillaries and antiangiogenic TKIs can affect thyroid homeostasis. In up to 36% of patients, an increase in thyroid-stimulating hormone and a decrease in the levels of the circulating thyroid hormones, indicative of hypothyroidism, have been observed after treatment with TKIs. Disturbance in thyroid function might result in fatigue (41).

Bleeding and disturbed wound healing

Anti-angiogenic therapy most probably disturbs the tight endothelial cell-platelet interaction. Loss of vascular integrity will cause bleeding complications, gastrointestinal perforations and disturbed wound and ulcer healing. Bleeding complications have been reported in up to 44% of