DOI:10.14753/SE.2013.1821

Utilization of Ketamine in spinal fusion, scoliosis, and microdiscectomy surgery- introducing a pharmaceutical care program

Ph.D. thesis

Bushra Abdul Hadi

Semmelweis University
Doctoral School of Pharmaceutical Sciences

Supervisor: Prof. Romána Zelkó, Ph.D., D.Sc.

Reviewers: Prof. Katalin Darvas Ph.D.
Prof. Gyöngyvér Soós Ph.D.

President of the Theoretical Exam Committe: Prof. György Bagdy, Ph.D., D.Sc.
Members of the Theoretical Exam Committe: Prof. Kornélia Tekes, Ph.D.
Dr. Judit Török, Ph.D.

Budapest

2012

DOI:10.14753/SE.2013.1821

CONTENT

DOI:10.14753/SE.2013.1821

DOI:10.14753/SE.2013.1821

DOI:10.14753/SE.2013.1821

DOI:10.14753/SE.2013.1821

1. ABBREVIATIONS

ABGs : Arterial blood gas

ADE : Adverse drug events

BP : Blood pressure

CPS : Cognitive pharmaceutical services

CPCF : Contractual frameworks for community pharmacy

DVT : Deep venous thrombosis

DRPs : Drug related problems

ECHO : Humanistic outcomes

GPs : General practitioners

G1 : group 1

G2 : group 2

G3 : group3

h : hour

HbA1C: Glycosylated haemoglobin

HDL : High Density Lipoprotein

HR : Heart rate

IDSA : Infectious Diseases Society of America

ICU : Intensive Care Unit

IV : Intravenous

LDL : Low Density Lipoprotein

MAP : Mean Arterial Pressure

min : Minute

mg : Milligram

ml : Milliliter

DOI:10.14753/SE.2013.1821

mmHg : Millimeter mercury

NMDA: N-methyl-D-aspartic acid

NPO : Non Per Oral

NHS : National Health Service

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

NS : Not Significant

N-V : Nausea - Vomiting

PACU : Post-Anesthesia Care Unit

Sc : Subcutaneous

SD : Standard Deviation

TIVA : Total Intravenous Anesthesia

UK : United Kingdom

UTIs : Urinary Tract Infections

Vs : Versus

WHO : World Health Organization

DOI:10.14753/SE.2013.1821

2. INTRODUCTION (LITERETURE REVIEW)

Intraoperative hemodynamic stability of a patient during surgery, and the requirements for subsequent analgesic consumption due to the severity of the postoperative pain, are all major challenges for the surgical team. Remifentanil is a highly selective opioid analgesic, acting on μ opiate receptors. It is used in combination with propofol as total intravenous anesthesia (TIVA) as it produces a more hypotensive effect as compared with other opioids (1). It has an ultra short duration of action as compared with other mu receptor agonists. This short duration of action is exemplified by the finding that no residual effects are observed as quickly as 5-10 minutes after stopping its administration. However this rapid reversal can be considered as a disadvantage of remifentanil in that the post-operative residual effect is minimal (2).

In contrast to the pharmacological effects of remifentanil, the blood pressure and pulse rate are frequently elevated when ketamine is administered. The elevation of blood pressure begins soon after its administration and reaches a maximum within a few minutes and usually returns to pre-anesthetic values within 15 minutes after injection (3).

Ketamine hydrochloride is an intravenous anesthetic. Its anesthetic and analgesic effects are mediated primarily by a non-competitive antagonism at N-methyl-D-aspartic acid (NMDA) receptors (4). Low-dose ketamine has a direct analgesic effect and also induces a postoperative morphine-sparing effect in some forms of surgery (5). Using a Low-dose infusion of ketamine (1 μg/ kg/min) has previously been used intra-operatively in different types of surgery (6,7) and used peri-operatively in major abdominal surgery (8, 9), and also to decrease post-operative intravenous morphine consumption (10, 11, 12). Many surveys have shown a high prevalence of significant pain after many types of surgery (13) and regulation of such postoperative pain is one of the most common therapeutic problems in hospitals (2).

To counter such pain, systemic opioids have been used but a major problem is that they can be associated with significant N-V side effects (14,15), nausea and vomiting (N-V) are the most common therapeutic problems in hospitals (2, 14) and many surveys have shown high

prevalence of significant pain and N-V after all types of major surgery (13, 16). Reducing the opiods dose can lead to a lower incidence of N-V (8).

Clinical pharmacists offer pharmaceutical care to improve patients' health, in addition to dispensing medications (17); Pharmaceutical care activities include three main components:

1. To try and ensure a patient is receiving optimal drug therapy for their condition whilst at the same time minimise drug related problems (18).

2. Patient education and counselling (illness, medication, healthy lifestyle, treatment goals, need for compliance with medication regimens and facilitating communication with physicians) (18).

3. Monitoring patient symptoms and outcomes (19, 20).

Why pharmacists are well suited for these tasks:

a. They have the educational background and knowledge and skills needed to identify and resolve drug-related problems,

b. While patients may have multiple physicians, if they are in the community receiving care they often patronize a single pharmacy,

c. Pharmacists are often the last health professional who patients see before taking a newly prescribed medication and

d. Pharmacists are rated highly by the public for their honesty and ethical standards (21).

Patients undergoing spinal fusion, scoliosis and lumbar microdiscectomy surgery experience very severe pain in the postoperative period, which may increase the incidence of postoperative morbidity and complications (2, 22, 23).

In this part of the thesis, I intended to examine the hypothesis that postoperative pain and morphine consumption would be reduced by using the infusion of a very small-dose of ketamine (1 μg/kg/min) both intra- and postoperatively. This drug was added to an intra-

operative remifentanil-based anesthesia regimen for spinal fusion, scoliosis, and lumbar microdiscectomy surgery. Furthermore, I evaluated the effect of ketamine on heamodynamic stability, N-V side effects, and its transient psychotic effects.

In the world literature, up to my best knowledge; clinical pharmacist has positive interventional role in the hospital, and in the community pharmacy in controlling chronic diseases as; blood pressure, blood cholesterol level, blood sugar level, and asthma (24, 25).

Furthermore the Infectious Diseases Society of America (IDSA) guidance considered clinical pharmacist as a central member of the team together with the infectious diseases physician (25). In addition to that, clinical pharmacist had positive impact on decreasing the expenditure (26, 27).

On the other hand little information exists about the clinical pharmacist intervention in the surgery room, PC Gordon et al. (2004) has advised that the SA Society of anesthesiologists should be involved with the pharmacist for different improvements (28).

Due to all the previous mentioned positive impacts of the clinical pharmacist in the different areas, I conducted a novel idea, by carrying out the clinical pharmacist intervention to the different anesthetics strategies during spinal fusion, scoliosis, and microdiscectomy surgery.

DOI:10.14753/SE.2013.1821

2.1. Ketamine

2.1.1. Mechanism of action

Ketamine is an established intravenous anesthetic agent, which was approved for clinical use in 1970 (28). It has anesthetic and analgesic effects which are mediated primarily by a non-competitive antagonism at N-methyl-D-aspartic acid (NMDA) receptors (3).

2.1.2. General uses of ketamine

Ketamine has been used to provide anesthesia or sedation to uncooperative children, as well as for battlefield emergencies (29, 30).

Furthermore, 'ketamine serves as a sedative and an analgesic agent for burn injuries' (31).

Tosun et al 2008 found that a 'propofol-ketamine combination provides effective sedation and analgesia during dressing changes in pediatric burn patients' (32).

There was increasing interest in the use of ketamine for asthma management.

Denmark TK et al 2006 suggested that for children experiencing severe asthma exacerbations, intravenous ketamine may be an effective temporizing measure to avoid exposing these children to the risks associated with mechanical ventilation (33).

It is used as an analgesic in cases of cancer (34), geriatric hip fracture (35), trauma (35) and neuropathic pain relief (36). Ketamine was used for neonate inguinal hernia (37).

It was not preferably applied for endoscope due to the increase in salivation it causes, leading to ventilatory obstruction that can evolve into laryngospasm; this result was confirmed by Cohen and Krauss 2006 (38). This risk can however be decreased by the administration of anticholinergic agents that reduce intraoral secretions (39).

Tomatir E and Esmaoglu A 2004 advised the use of a low dose of ketamine for pediatric magnetic resonance imaging before induction on propofol anesthesia (35).

Applying ketamine as a mouth wash was used by Canbay O. et al (2008). He agreed that 'ketamine gargle significantly reduced the incidence and severity of postoperative sore throat' (40). Nayar R. and Sahajanand H. 2008 (41), and Leykin Y et al. 2006 (42) proved

the safety of using ketamine during labor, in caesarean section in combination with thiopentone; while they agreed that it is not safe for use as a solo drug.

2.1.3. Ketamine effect on hemodynamic stability

The blood pressure and the pulse rate are frequently elevated following the administration of ketamine alone. The elevation of blood pressure begins shortly after its administration, reaching a maximum within a few minutes and usually returns to pre-anesthetic values within 15 minutes after cessation of its administration (3, 42). Accordingly Hatano S et al (1976) in his study confirmed excellent results for using ketamine for open heart surgery (43). Furthermore, Haas DA et al (38) in their study confirmed that ketamine can help in avoiding cardiovascular depression. On the other hand, ketamine should be avoided in patients with coronary artery disease, uncontrolled hypertension, congestive heart failure, and arterial aneurysms (37).

2.1.4. Uses of low dose ketamine post-operatively as an analgesic

Positive results were achieved after using low doses ketamine post-operatively as an analgesic (41). Filippia et al (44) found that pain (preoperative, postoperative and chronic) can be managed with ketamine in a wide variety of surgical procedures. When ketamine was administered intravenously during anesthesia in adults, it decreases postoperative pain intensity and morphine consumption, and delays the time to first request of rescue analgesic therapy for up to 48 hours (36, 44). Ketamine was used after large variety of surgeries , Suppa E et.al 2012 have used low-dose S-Ketamine infusion as "preventive" pain treatment for cesarean section with spinal anesthesia (45), where Beena Parikh 2011 have used it for same purpose after renal surgery (46). Ketamine provided effective analgesia effect in patients undergoing major digestive surgery (46), and for women undergoing abdominal hysterectomy (48).

DOI:10.14753/SE.2013.1821

2.1.5. The influence of low dose ketamine on the total morphine consumption, and then on nausea and vomiting side effects

Low-dose ketamine (1 μg/kg/min) was previously tested intra-operatively peri-operatively in major abdominal surgery (5) to decrease post-operative intravenous morphine consumption (8, 9, 14, 49-52). Systemic opioids can be associated with significant N-V side effects, and lowering the morphine dose leads to a lower incidence of N-V (8).

2.1.6. Management methods used for post-operative pain in spinal fusion, scoliosis, and microdiscectomy surgery

Patients undergoing spinal fusion, scoliosis, and microdiscectomy surgery experience severe pain in the postoperative period, which may increase the incidence of postoperative morbidity and complications (53-56). Different methods have been used to reduce the postoperative pain. Urban MK et. al (2002) have applied intrathecal morphine to reduce the post-operative pain in spinal fusion surgery (53). Bourke DL et al. 1992 have used Epidural opioids during laminectomy surgery for postoperative pain (57), Thienthong S et al. 2004 have used single dose lornoxicam after spinal surgery (58), and Michael A E et al (2006) have confirmed that good postoperative pain control is essential and requires a multimodal approach (59). Table 1 summarizes the effect and side effect of ketamine.

DOI:10.14753/SE.2013.1821

Table 1 Effects and side effects of ketamine (29- 59)

Ketamine	Effects	Side Effects by Body System
	• Anesthetic or sedative to uncooperative children, battlefield emergencies. • Burn injuries, asthma management, analgesic in cases of cancer, geriatric hip fracture, trauma, neuropathic pain relief. • Neonate inguinal hernia, pediatric magnetic resonance imaging, gargles for postoperative sore throat, during labor, in caesarean section in combination with thiopentone. • Elevate blood pressure and pulse rate. • Low dose ketamine post-operatively as an analgesic. • The influence of low dose ketamine on the total morphine consumption, and then on nausea and vomiting side effect.	• Cardiovascular: elevated blood pressure and pulse rate, arrhythmia has also been reported. • Respiratory: severe depression of respiration or apnea may occur following rapid intravenous administration of ketamine. • Ocular: diplopia, nystagmus, and a slight elevation in intraocular pressure. • Gastrointestinal: anorexia, nausea, and vomiting. • Musculoskeletal: enhanced skeletal muscle tone, sometimes resembling seizures. • Local: pain and exanthema at the injection site. • Dermatologic: transient erythema and/or morbilliform rash. • Psychiatric: anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychotic episodes, withdrawal syndrome.

DOI:10.14753/SE.2013.1821

2.2. Clinical pharmacy and pharmaceutical care

2.2.1. Definition and development of pharmaceutical care

Within the last decades, the role of the pharmacist and of pharmacy practice have moved from that of drug manufacturing and technical dispensing to a more cognitive role with patient orientation (17). Repeated pharmaceutical care was first defined by Mikeal et al. in 1975 (60) as "the care that a given patient requires and receives which assures safe and rational drug usage".

The concept of pharmaceutical care focuses on the process of 'using a drug', bearing in mind that the dispensing of a drug is neither the beginning nor the end of this process (18, 61).

According to the definition of Hepler and Strand (62, 63), pharmaceutical care is "the responsible provision of medicine therapy for the purpose of definite outcomes that improve a patient's quality of life." Pharmaceutical care is based on a relationship between the patient and the pharmacist who accepts responsibility for the patient. The concept implies the active participation of the patient in making decisions regarding his/her pharmacotherapy and the interdisciplinary cooperation of healthcare providers, and gives priority to the direct benefit of the patient.

Assessments of drug-related problems (DRPs), development of a care plan and its evaluation, as well as a continuous follow-up are important steps of the pharmaceutical care process (18, 64).

Patient expectations and desired quality of life are important factors to ensure the best possible medication outcome, and to possibly prevent recurrence of disease. Pharmaceutical care is an indispensable element of patient centered healthcare and requires a change of traditional professional attitudes, a re-engineering of the pharmacy environment, the use of new technologies, and the acquisition of knowledge as well as skills in the areas of patient

assessment, clinical information, communication, adult teaching, and psychosocial aspects of care (18).

The term ‘pharmaceutical care’ has established itself as a philosophy of practice, with the patient and the community as the primary beneficiaries of the pharmacist’s actions. The concept is particularly relevant to special groups such as the elderly, mothers and children, and chronically ill patients. The model of pharmaceutical care is perhaps most advanced in the United Kingdom (UK) as evidenced by the new National Health Service (NHS) contractual frameworks for community pharmacy CPCF) (65). Clinical pharmacy is a commonly used term in pharmacy practice and in pharmacy literature.

It is a health specialty which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices (66).

The term includes all services performed by pharmacists practicing in hospitals, community pharmacies, nursing homes, home based care services, clinics, and any other setting where medicines are prescribed and used. The term ‘clinical’ does not necessarily imply an activity implemented in a hospital setting. A community pharmacist as well as a hospital practitioner may perform clinical activities. Clinical pharmacists activities aim at maximizing the clinical effect of medicines (i.e. using the most effective treatment for each type of patient), minimizing the risk of treatment-induced adverse events (i.e. monitoring the therapy course and the patient’s compliance with therapy), and minimizing the expenditures for pharmacological treatments (66) driven by the national healthcare systems and the patients (i.e. trying to provide the best treatment for the greatest number of patients). Medication reviews on individual patient level form a central part of this process. A literature review found that clinical pharmacy interventions in inpatient medical care contribute to improved patient outcomes (19).

A number of studies have demonstrated the clinical and economic benefits of clinical pharmacy interventions in hospital and primary care settings (20)

DOI:10.14753/SE.2013.1821

The World Health Organization (WHO) and others consider community pharmacists to be ideally positioned to play important roles in facilitating improved patient adherence by, among others, providing patients with cognitive pharmaceutical services (CPS) that include the provision of appropriate health-related information and counseling to promote self-care and the correct use of medicines (67).

There is ample evidence that pharmaceutical care and CPS have been successfully applied by pharmacists across a range of disease entities and in different pharmacy practice settings (68). Comprehensive or cognitive pharmacy services involve activities both to secure good health and to avoid ill-health in the population. When ill-health is treated, it is necessary to assure quality in the process of using medicines in order to achieve maximum therapeutic benefit and avoid untoward side-effects. This presupposes the acceptance by pharmacists of shared responsibility with other professionals and with patients for the outcome of therapy (17).

2.2.2. Effectiveness of pharmaceutical care

An evidence report issued in 2004 by the Danish College of Pharmacy Practice (Pharmakon) (69) about the follow-up on outcomes of drug therapy (Pharmaceutical Care) covered 44 studies between 1990 and October 2003 (24). This report showed strong evidence that pharmaceutical care can positively influence clinical parameters (blood pressure [BP], blood sugar, and cholesterol) and that there is a positive influence on health-related quality of life of asthma patients and patients with elevated cholesterol levels, hypertension, and diabetes. However, three out of five studies in elderly patients showed no difference between intervention and control groups. There is a tendency that programs for the elderly do not affect drug use, and the authors found evidence for the cost effectiveness of pharmaceutical care programs, patient satisfaction, and increased adherence (but not among the elderly), but evidence of improved knowledge was inconsistent. They concluded that pharmaceutical care programs can contribute to solving DRPs of clinical significance and adverse drug events (ADE), that the acceptance rate among general practitioners (GPs)

and patients is high, and that pharmaceutical care promotes more rational drug use among patients with elevated cholesterol levels and asthma patients.

A critical review, published by Blenkinsopp et al. in 2005 (70), about enhanced community pharmacy-based diabetes care included 17 studies between 1990 and 2003. They found only a few trials of community pharmacy-based interventions to improve diabetes care. However, the authors concluded that there is limited evidence of effectiveness of community pharmacy-based interventions in diabetes care.

A systematic review by Roughead et al. (71) 2005 looking at the effectiveness of pharmaceutical care services in the community or outpatient setting on patient outcomes included 22 randomized, controlled trials from 1990 to 2003 (71) and provided an evidence base for the improvement of medication use. Within this review, studies showed improved surrogate endpoints such as changes in blood pressure, glycosylated hemoglobin (HbA1C), lipids, and peak expiratory flow rates (24).

Zermansky et al. (25) concluded that pharmacists' recommendations by clinical pharmacists were usually accepted and that there was a reduction in the number of falls but no changes or improvements of costs, hospitalizations, and mortality.

Bond et al. (2007) (72) reported that pharmacist-led services were more expensive than standard care and that no change in the proportion of patients receiving appropriate medication was observed.

The reviews identified in the literature search concerning the pharmacist role found that pharmacist has significant positive effects on HbA1c levels (73), systolic BP (74), and total cholesterol (75) as well as on low-density lipoprotein (LDL) cholesterol and triglyceride levels. In addition, there is evidence that clinical pharmacy interventions can reduce the occurrence of DRPs (76).

However, no improvements on high-density lipoprotein (HDL) cholesterol levels (75), diastolic BP, and adherence (14, 8, 53) were found. Moreover, no effects were found on mortality and all-case hospital admission (77), and there was unclear evidence about effects

on quality of life (75, 77) Overall, there the effectiveness of pharmaceutical care remains unclear. However, several studies and reviews could show benefit and evidence for different activities considering economic, clinical, and humanistic outcomes (ECHO). Furthermore, patients and pharmacists as well as physicians in many cases were satisfied with pharmaceutical care services. Further research with larger intervention studies with improved quality of design is needed.

Tonna et al. (2008) reviewed the literature on clinical pharmacist participation as a key member of multi disciplinary antimicrobial team, including 16 studies (USA [9 studies], UK [4 studies], Canada, France, and Switzerland, each 1 study). Pharmacist roles included guideline development, formulary management, changing administration route from intravenous to oral, assessing program outcomes through monitoring of drug usage, participating in ward rounds, and streamlining of the primary empirical antimicrobial therapy (78). Interestingly, the 2007 Infectious Diseases Society of America (IDSA) guidance considered clinical pharmacist as a central member of the team together with the infectious diseases physician (26).

2.2.3. Three main components of pharmaceutical care

2.2.3.1. Ensure patient is receiving optimal drug therapy (minimise drug related problems)

2.2.3.1.1. Drug-related problems (definition & role of clinical pharmacist)

A drug-related problem is defined by Strand et al, and Segal et al in 1990, and 1999 respectively (79, 80) as "an undesirable patient experience that involves drug therapy and that actually or potentially interferes with the desired patient outcome ,and as "a circumstance of drug therapy that may interfere with a desired therapeutic objective" Table 2 shows the definition and terms associated with problems of pharmacotherapy (80). Table 3 shows classification of medication error severity (81). Table 4 shows the circumstance of drug therapy that may interfere with a desired therapeutic objective (82).

DOI:10.14753/SE.2013.1821

Table 2 Definition and terms associated with problems of pharmacotherapy (DRPs) (80)

Adverse drug event	Any injury related to the use of a drug, even if the causality of this relation is not proven
Adverse drug reaction	Any response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological functions
Medication error	Any error in the medication process (prescribing , dispensing, administering of drugs), whether there are adverse consequences or not

Table 3 Potential severity assessment code (81)

Rating	Description	Categories used in analysis
1	Incident is likely to have little or no effect on the patient	Minor error
2	Incident is likely to lead to an increase in level of care, for example, review , investigations, or referral to another clinician	Minor error
3	Incident is likely to lead to permanent reduction in bodily functioning leading to for example , increasing length of stay , surgical intervention	Serious error
4	Incident is likely to lead to permanent loss of function	Serious error
5	Incident is likely to lead to death	Serious error

DOI:10.14753/SE.2013.1821

Table 4 Circumstance of drug therapy that may interfere with a desired therapeutic objective (82)

Types of drug-related problems (circumstance of drug therapy that may interfere with a desired therapeutic objective)
Uncertainty about/ lack of knowledge of the aim/
Function of drug
Underuse of medication
Overuse of medication
Other dosage problem
Drug duplication
Drug–drug interaction
Therapy failure
Side effect
Difficulty swallowing tablet/capsule
Difficulty opening container
Other practical problem, such as incorrect use of
Administrating device
Language deficiency/ understanding disability
Prescribing error, such as incorrect or omitted data on the prescribed drug
Other drug related problem, such as use of a drug for the wrong indication, contraindications

The identification, prevention and solution of drug related problems, is the core process of pharmaceutical care, aiming to improve patient outcomes (83, 84).

DOI:10.14753/SE.2013.1821

2.2.3.1.2. Consequences of non-optimal drug therapy

Drug-related problems in general (75) have shown to cause hospital admissions.
In meta-analysis (75) adverse drug reactions have shown to account for approximately five percent of all hospital admissions. In a subgroup analysis, conducted by Beijer et al (84) the odds for elderly people to be hospitalized because of adverse drug reactions was four times higher than for younger ones. Adverse drug-reactions and events have further shown to increase the length of hospital stay the cost of hospital stay as well as mortality (85).

2.2.3.1.3. Methods aiming to optimize drug therapy

2.2.3.1.3.1. Medication histories

Medication histories in the hospital records are often incomplete (86). An accurate medication history, including an updated medication list is a prerequisite for the physician to make appropriate diagnostic and prescribing decisions during the hospital stay. Given the consequences of medication errors and its potential for prevention, there is a need to identify effective interventions that can reduce medication errors at admission. The medication history interview is a vital tool in identifying medication errors (87) and giving insight into the patient's medication taking experience, patient understanding of their medications and patient motivation for compliance. It has been shown that trained clinical pharmacists obtain more complete medication histories, compared to other health care professionals (88). Clinical pharmacists conducting medication histories at admission and drug information sessions with the patient at discharge have shown to reduce the numbers of readmissions to hospital (88).

2.2.3.1.3.2. Medication review

A structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems and reducing waste (87).

Many people are prescribed multiple, long term medications and it is therefore a major challenge to ensure that these patients get the maximum benefit from all their medicines.

In a US study by Bootman et al (89) it was estimated that for every dollar spent on medicines, $1.33 in health care resources were consumed in the treatment of drug-related problems and that consultant pharmacist significantly reduced cost related to the treatment of drug-related problems. In a Swedish study (90) medication reviews have shown to decrease the prescribing of inappropriate drugs, e.g. psychotics, benzodiazepine hypnotics and antidepressants.

Clinical medication reviews have shown to decrease the number of used drugs (26), decrease the number of drug-related problems (91), decrease costs (26), decrease the length of stay at the hospital (92), decrease the number of adverse drug events (93) increase the quality of life (94) and decrease the number of readmissions to hospital (94), with no impact on mortality (95).

2.2.3.2. Patient education and counselling (illness, medication, healthy lifestyle, treatment goals, need for compliance with medication regimens, facilitating communication with physicians)

2.2.3.2.1. General Patient education and counselling

Subish P. et al (2006) have summarised drug counselling points for chronic diseases (96), like: hypertension, diabetes, coronary heart disease, dyslipidemia, asthma, epilepsy, rheumatoid arthritis. He reviewed the positive intervention outcome for different articles from 1977-2002.

In (2011) Sarah J. et al (97) have talked about the impact of pharmacist patient counselling in relation to drug therapy problems, like: patient taking unnecessary drug therapy, or needs additional therapy, needs more effective drug, synergistic therapy, increase or decrease the dose to reach the goal, adverse drug reaction, and patient compliance.

On the other hand latest paper was written about face-to-face counselling sessions with a community pharmacist at the beginning of statin therapy by Taitel M. et al. (2012) (98), demonstrated the risk of no adherence and discontinuation of drug; helped patients establish a routine of daily self-medication and potentially improved their long-term clinical outcomes.

2.2.3.2.2. Patient perioperative education and counselling

The perioperative period extends from the preoperative day through the operation and into the postoperative recovery. Proper perioperative management helps to prevent or minimize complications, to reduce postoperative pain, and to accelerate recovery. The components of perioperative medication management are as follows:

Nafisa K et al (2008) (99) talked about the components of perioperative medication management, they summarized the management in the following points:

- Accurate documentation of preoperative medication
- Established decisions on stopping medications prior to surgery
- Monitoring of appropriate chemistry study results to determine dosages and the occurrence of adverse effects
- Appropriate management of pain
- Administration of adjunctive medications
- Use of appropriate formulations and alternative products when needed
- Review of discharge medications to ensure discontinuation of surgery-specific drugs (eg, anticoagulants, analgesics) to avoid polypharmacy.

DOI:10.14753/SE.2013.1821

2.2.3.2.2.1. Preoperative counseling

Preoperative care involves many components, and may be done the day before surgery in the hospital, or during the weeks before surgery on an outpatient basis (100).

Physical preparation

Physical preparation may consist of a complete medical history and physical exam, including the patient's surgical and anesthesia background. Laboratory tests may include complete blood count, electrolytes, prothrombin time, activated partial thromboplastin time, and urinalysis. The patient will most likely have an electrocardiogram if he or she has a history of cardiac disease, or is over 50 years of age. A chest x ray is done if the patient has a history of respiratory disease. Part of the preparation includes assessment for risk factors that might impair healing, such as nutritional deficiencies, steroid use, radiation or chemotherapy, drug or alcohol abuse, or metabolic diseases such as diabetes. The patient should also provide a list of all medications, vitamins, and herbal or food supplements that he or she uses. Tables 5-8 outline the perioperative management of NSAIDs and drug management of patients with coronary artery disease, hypertension, diabetes and hypothyroidism respectively (99).

DOI:10.14753/SE.2013.1821

Table 5 Perioperative Management of NSAIDs (99)

Drug	Day Before Surgery	Day of Surgery	During Surgery	After Procedure	Substitute Drug if Needed
NSAIDs with long half-life	Discontinue 1 week before surgery			IM preparation until patient is on oral liquids	
NSAIDs with short half-life	Discontinue 2-3 days before surgery			IM preparation until patient is on oral liquids	

DOI:10.14753/SE.2013.1821

Table 6 Outline of Perioperative Drug Management of Patients with Coronary Artery (99)

Drug	Day Before Surgery	Day of Surgery	During Surgery	After Procedure	Drug
Nitroglycerin	Usual dose	Usual dose	IV infusion if frank ischemia	Continue IV dose if needed or until medication can be taken PO	Nitroglycerin
Beta-blockers	Usual dose	Usual dose plus beta-blocker protocol	Usual dose plus beta-blocker protocol	Usual dose plus beta-blocker protocol	Beta-blockers
Calcium channel blockers	Usual dose	Usual dose morning of surgery	Usual dose morning of surgery	Continue IV dose until medication can be taken PO	Calcium channel blockers
Aspirin	Discontinue 1 week before surgery			Restart postoperatively at discretion of surgeon	Aspirin
Ticlopidine	Discontinue 1 week before surgery			Restart postoperatively at discretion of surgeon	Ticlopidine

DOI:10.14753/SE.2013.1821

Table 7 Perioperative Drug Management for Patients with Hypertension (99)

Drug	Day Before Surgery	Day of Surgery	During Surgery	After Procedure
Beta-blockers + Calcium channel blockers + ACE inhibitors	Usual dose	Usual dose on morning of surgery with sip of water	IV bolus or infusion (usually not required)	Continue IV dose until medication can be taken PO
Diuretics	Stop day before		IV beta-blockers/IV calcium channel blockers	Restart when patient on oral liquids
Potassium supplements	Stop day before; consider checking potassium level			Restart when patient on oral liquids
Central-acting sympatholytics	Usual dose	Usual dose on morning of surgery with sip of water	Transdermal clonidine/IV methyldopa	Restart when patient on orals liquids
Peripheral sympatholytics + Alpha-blockers + Vasodilators	Usual dose	Usual dose on morning of surgery with sip of water	Any IV formulation (usually not required)	Restart when patient on oral liquids

Table 8 Perioperative Medication Management for Patients with Diabetes and Hypothyroidism (99)

Drug	Day Before Surgery	Day of Surgery	During Surgery	After Procedure
Oral hypoglycemic	Usual dose	Omit dose	Insulin (SC or IV)	Insulin until patient is no longer NPO
Insulin	Usual dose	Omit dose	Insulin (SC or IV)	Usual dose
Thyroxin	Usual dose	Usual dose on morning of surgery with sip of water		Restart the dose when patient is no longer NPO

Supplements are often overlooked, as it may cause adverse effects when used with general anesthetics (e.g., St. John's wort, valerian root). Some supplements can prolong bleeding time (e.g., garlic, gingko biloba).

Latex allergy has become a public health concern. Latex is found in most sterile surgical gloves, and is a common component in other medical supplies including general anesthesia masks, tubing, and multi-dose medication vials. Children with disabilities are particularly susceptible. This includes children with spina bifida, congenital urological abnormalities, cerebral palsy, and dandy-walker syndrome as a result of early, frequent surgical exposure. There is currently no cure available for latex allergy. The best treatment is prevention, but immediate symptomatic treatment is required if the allergic response occurs. Every patient should be assessed for a potential latex reaction. Patients with latex sensitivity should have

DOI:10.14753/SE.2013.1821

their chart flagged with a caution label. Latex-free gloves and supplies must be used for anyone with a documented latex allergy.

Bowel clearance may be ordered if the patient is having surgery of the lower gastrointestinal tract (99).

Psychological preparation

Patients are often fearful or anxious about having surgery. It is often helpful for them to express their concerns to health care workers. The family needs to be included in psychological preoperative care. In some cases, the procedure may be postponed until the patient feels more secure.

Children may be especially fearful. They should be allowed to have a parent with them as much as possible, as long as the parent is not demonstrably fearful and contributing to the child's apprehension. Children should be encouraged to bring a favorite toy or blanket to the hospital on the day of surgery.

Patients and families who are prepared psychologically tend to cope better with the patient's postoperative course. Preparation leads to superior outcomes since the goals of recovery are known ahead of time, and the patient is able to manage postoperative pain more effectively (99).

Informed consent

The patient's or guardian's written consent for the surgery is a vital portion of preoperative care. By law, the physician who will perform the procedure must explain the risks and benefits of the surgery, along with other treatment options. It is important that the patient understands everything he or she has been told. Sometimes, patients are asked to explain what they were told so that the health care’s professional can determine how much is understood.

DOI:10.14753/SE.2013.1821

Patients who are mentally impaired, heavily sedated, or critically ill are not considered legally able to give consent. In this situation, the next of kin (spouse, adult child, adult sibling, or person with medical power of attorney) may act as a surrogate and sign the consent form. Children under age 18 must have a parent or guardian sign (99).

Preoperative teaching

Preoperative teaching includes instruction about the preoperative period, the surgery itself, and the postoperative period.

Instruction about the preoperative period deals primarily with the arrival time, where the patient should go on the day of surgery, and how to prepare for surgery. For example, patients should be told how long they should be NPO (nothing by mouth), which medications to take prior to surgery, and the medications that should be brought with them (such as inhalers for patients with asthma).

Instruction about the surgery itself includes informing the patient about what will be done during the surgery, and how long the procedure is expected to take. The patient should be told where the incision will be. Children having surgery should be allowed to "practice" on a doll or stuffed animal. It may be helpful to demonstrate procedures on the doll prior to performing them on the child. It is also important for family members (or other concerned parties) to know where to wait during surgery, when they can expect progress information, and how long it will be before they can see the patient.

Knowledge about what to expect during the postoperative period is one of the best ways to improve the patient's outcome. Instruction about expected activities can also increase compliance and help prevent complications. This includes the opportunity for the patient to practice coughing and deep breathing exercises, use an incentive spirometer, and practice splinting the incision. Additionally, the patient should be informed about early ambulation (getting out of bed). The patient should also be taught that the respiratory interventions decrease the occurrence of pneumonia, and that early leg exercises and ambulation decrease the risk of blood clots.

DOI:10.14753/SE.2013.1821

Patients hospitalized postoperatively should be informed about the tubes and equipment that they will have. These may include multiple intravenous lines, drainage tubes, dressings, and monitoring devices. In addition, they may have sequential compression stockings on their legs to prevent blood clots until they start ambulating.

Patients may receive educational materials such as handouts and video tapes, so that they will have a clear understanding of what to expect postoperatively (99).

Pain management is the primary concern for many patients having surgery. Preoperative instruction should include information about the pain management method that they will utilize postoperatively. Patients should be encouraged to ask for or take pain medication before the pain becomes unbearable, and should be taught how to rate their discomfort on a pain scale. This instruction allows the patients, and others who may be assessing them, to evaluate the pain consistently. If they will be using a patient-controlled analgesia pump, instruction should take place during the preoperative period. Use of alternative methods of pain control (distraction, imagery, positioning, mindfulness meditation, music therapy) may also be presented.

Finally, the patient should understand long-term goals such as when he or she will be able to eat solid food, go home, drive a car, and return to work.

The anticipated outcome of preoperative care is a patient who is informed about the surgical course, and copes with it successfully. The goal is to decrease complications and promote recovery (99).

2.2.3.2.2.2. Postoperative care

Postoperative care involves assessment, diagnosis, planning, intervention, and outcome evaluation. The extent of postoperative care required depends on the individual's pre-surgical health status, type of surgery, and whether the surgery was performed in a day-surgery setting or in the hospital. Patients who have procedures done in a day-surgery center usually require only a few hours of care by health care professionals before they are

discharged to go home. If postanesthesia or postoperative complications occur within these hours, the patient must be admitted to the hospital. Patients who are admitted to the hospital may require days or weeks of postoperative care by hospital staff before they are discharged (101).

Postanesthesia care unit (PACU)

The patient is transferred to the PACU after the surgical procedure, anesthesia reversal, and extubation (if it was necessary). The amount of time the patient spends in the PACU depends on the length of surgery, type of surgery, status of regional anesthesia (e.g., spinal anesthesia), and the patient's level of consciousness. Rather than being sent to the PACU, some patients may be transferred directly to the critical care unit. For example, patients who have had coronary artery bypass grafting are sent directly to the critical care unit.

In the PACU, the anesthesiologist or the nurse anesthetist reports on the patient's condition, type of surgery performed, type of anesthesia given, estimated blood loss, and total input of fluids and output of urine during surgery. The PACU nurse should also be made aware of any complications during surgery, including variations in hemodynamic (blood circulation) stability.

The patient is discharged from the PACU when he or she meets established criteria for discharge, as determined by a scale. One example is the Aldrete scale, which scores the patient's mobility, respiratory status, circulation, consciousness, and pulse oximetry. Depending on the type of surgery and the patient's condition, the patient may be admitted to either a general surgical floor or the intensive care unit. Since the patient may still be sedated from anesthesia, safety is a primary goal. The patient's call light should be in the hand and side rails up. Patients in a day surgery setting are either discharged from the PACU to the unit, or are directly discharged home after they have urinated, gotten out of bed, and tolerated a small amount of oral intake (101).

DOI:10.14753/SE.2013.1821

First 24 hours

After the hospitalized patient transfers from the PACU, if the patient reports "hearing" or feeling pain during surgery (under anesthesia) the observation should not be discounted. The anesthesiologist or nurse anesthetist should discuss the possibility of an episode of awareness under anesthesia with the patient. Vital signs, respiratory status, pain status, the incision, and any drainage tubes should be monitored every one to two hours for at least the first eight hours. Body temperature must be monitored, since patients are often hypothermic after surgery, and may need a warming blanket or warmed IV fluids. Respiratory status should be assessed frequently, including assessment of lung sounds (auscultation) and chest excursion, and presence of an adequate cough. Fluid intake and urine output should be monitored every one to two hours. If the patient does not have a urinary catheter, the bladder should be assessed for distension, and the patient monitored for inability to urinate. The physician should be notified if the patient has not urinated six to eight hours after surgery. If the patient had a vascular or neurological procedure performed, circulatory status or neurological status should be assessed as ordered by the surgeon, usually every one to two hours. The patient may require medication for nausea or vomiting, as well as pain.

Patients with a patient-controlled analgesia pump may need to be reminded how to use it. If the patient is too sedated immediately after the surgery, the nurse may push the button to deliver pain medication. The patient should be asked to rate his or her pain level on a pain scale in order to determine his or her acceptable level of pain. Controlling pain is crucial so that the patient may perform coughing, deep breathing exercises, and may be able to turn in bed, sit up, and, eventually, walk.

Effective preoperative teaching has a positive impact on the first 24 hours after surgery. If patients understand that they must perform respiratory exercises to prevent pneumonia; and that movement is imperative for preventing blood clots, encouraging circulation to the extremities, and keeping the lungs clear; they will be much more likely to perform these tasks. Understanding the need for movement and respiratory exercises also underscores the

DOI:10.14753/SE.2013.1821

importance of keeping pain under control. Respiratory exercises (coughing, deep breathing, and incentive spirometry) should be done every two hours. The patient should be turned every two hours, and should at least be sitting on the edge of the bed by eight hours after surgery, unless contraindicated (e.g., after hip replacement). Patients who are not able to sit up in bed due to their surgery will have sequential compression devices on their legs until they are able to move about. These are stockings that inflate with air in order to simulate the effect of walking on the calf muscles, and return blood to the heart. The patient should be encouraged to splint any chest and abdominal incisions with a pillow to decrease the pain caused by coughing and moving. Patients should be kept NPO (nothing by mouth) if ordered by the surgeon, at least until their cough and gag reflexes have returned. Patients often have a dry mouth following surgery, which can be relieved with oral sponges dipped in ice water or lemon ginger mouth swabs.

Patients who are discharged home are given prescriptions for their pain medications, and are responsible for their own pain control and respiratory exercises. Their families should be included in preoperative teaching so that they can assist the patient at home. The patient can call the physician, or manage home care service if any complications or uncontrolled pain arise (101).

After 24 hours

After the initial 24 hours, vital signs can be monitored every four to eight hours if the patient is stable. The incision and dressing should be monitored for the amount of drainage and signs of infection. The surgeon may order a dressing change during the first postoperative day; this should be done using sterile technique. For home-care patients this technique must be emphasized.

The hospitalized patient should be sitting up in a chair at the bedside and ambulating with assistance by this time. Respiratory exercises are still being performed every two hours, and incentive spirometry values should improve. Bowel sounds are monitored, and the patient's

diet gradually increased as tolerated, depending on the type of surgery and the physician's orders.

The patient should be monitored for any evidence of potential complications, such as leg edema, redness, and pain (deep vein thrombosis), shortness of breath (pulmonary embolism), dehiscence (separation) of the incision, or ileus (intestinal obstruction). The surgeon should be notified immediately if any of these occur. If dehiscence occurs, sterile saline-soaked dressing packs should be placed on the wound (101).

2.2.3.3. Monitoring patient outcomes

Postoperative care begins in the recovery room and continues throughout the recovery period. Critical concerns are airway clearance, pain control, mental status, and wound healing. Other important concerns are preventing urinary retention, constipation, deep venous thrombosis, and BP variability (high or low). For patients with diabetes, plasma glucose levels are monitored closely by finger-stick testing every 1 to 4 h until patients are awake and eating, because better glycemic control improves outcome (102).

2.2.3.3.1. Airway

Most patients are extubated before leaving the operating room and soon become able to clear secretions from their airway. Patients should not leave the recovery room until they can clear and protect their airway (unless they are going to an ICU). After intubation, patients with normal lungs and trachea may have a mild cough for 24 h after extubation; for smokers and patients with a history of bronchitis, postextubation coughing lasts longer. Most patients who have been intubated, especially smokers and patients with a lung disorder, benefit from an incentive inspirometer.

Postoperative dyspnea may be caused by pain secondary to chest or abdominal incisions (nonhypoxic dyspnea) or by hypoxemia. Hypoxemia secondary to pulmonary dysfunction

is usually accompanied by dyspnea, tachypnea, or both; however, over sedation may cause hypoxemia but blunt dyspnea, tachypnea, or both. Thus, sedated patients should be monitored with pulse oximetry or capnometry. Hypoxic dyspnea may result from atelectasis or, especially in patients with a history of heart failure or chronic kidney disease, fluid overload. Whether dyspnea is hypoxic or no hypoxic must be determined by pulse oximetry and sometimes ABG; chest x-ray can help differentiate fluid overload from atelectasis. Hypoxic dyspnea is treated with oxygen. Nonhypoxic dyspnea may be treated with anxiolytics or analgesics (102).

2.2.3.3.2**.** Pain

Pain control may be necessary as soon as patients are conscious. Opioids are typically the first-line choice and can be given orally or parenterally.

If patients do not have a renal disorder or a history of GI bleeding, giving NSAIDs at regular intervals may reduce breakthrough pain, allowing the opioid dosage to be reduced (101, 102).

2.2.3.3.3. Mental status

All patients are briefly confused when they come out of anesthesia. The elderly, especially those with dementia, are at risk of postoperative delirium, which can delay discharge and increase risk of death. Risk of delirium is high when anticholinergics are used. These drugs sometimes are used before or during surgery to decrease upper airway secretions, but they should be avoided whenever possible. Opioids, given postoperatively, also may cause delirium, as can high doses of H_2 blockers. The mental status of elderly patients should be assessed frequently during the postoperative period. If delirium occurs, oxygenation should be assessed, and all nonessential drugs should be stopped. Patients should be mobilized as they are able, and any electrolyte or fluid imbalances should be corrected (102).

2.2.3.3.4. Wound care

The surgeon must individualize care of each wound, but the sterile dressing placed in the operating room is generally left intact for 24 h unless signs of infection (e.g., increasing pain, erythema, drainage) develop. After 24 h, the site should be checked twice/day, if possible, for signs of infection. If they occur, wound exploration and drainage of abscesses, systemic antibiotics, or both may be required. Topical antibiotics are usually not helpful. A drain tube, if present, must be monitored for quantity and quality of the fluid collected. Sutures, skin staples, and other closures are usually left in place 7 days or longer depending on the site and the patient. Face and neck wounds may be superficially healed in 3 days; wounds on the lower extremities may take weeks to heal to a similar degree (102).

2.2.3.3.5. Deep venous thrombosis (DVT) prophylaxis

Risk of DVT after surgery is small, but, because consequences can be severe and risk is still higher than in the general population, prophylaxis is often warranted. Surgery itself increases coagulability. Prophylaxis for DVT usually begins in the operating room was heparin may be started shortly after surgery, when risk of bleeding has decreased. Patients should begin moving their limbs as soon as it is safe for them to do so (102).

2.2.3.3.6. Fever

A common cause of fever is a high metabolic rate that occurs with the stress of an operation. Other causes include pneumonia, UTIs, and wound infections. Incentive spirometry and periodic coughing can help decrease risk of pneumonia (102).

2.2.3.3.7. Urinary retention and constipation

Urinary retention and constipation are common after surgery. Causes include use of anticholinergics or opioids, immobility, and decreased oral intake. Patients must be monitored for urinary retention. Straight catheterization is typically necessary for patients who have a distended bladder and are uncomfortable or who have not urinated for 6 to 8 h after surgery; Credé's maneuver sometimes helps and may make catheterization

unnecessary. Chronic retention is best treated by avoiding causative drugs and by having patients sit up as often as possible. Bethanechol 5 to 10 mg can be tried in patients unlikely to have any bladder obstruction and who have not had a laparotomy; doses can be repeated every hour up to a maximum of 50 mg/day. Sometimes an indwelling bladder catheter is needed, especially if patients have a history of retention or a large initial output after straight catheterization. Constipation is treated by avoiding causative drugs and, if patients have not had GI surgery, by giving stimulant laxatives (e.g., bisacodyl, sienna, cascara) (102).

2.2.3.3.8. Loss of muscle mass (sarcopenia)

Loss of muscle mass (sarcopenia) and strength occur in all patients in whom bed rest is prolonged. With complete bed rest, young adults lose about 1% of muscle mass/day, but the elderly lose up to 5%/day because growth hormone levels decrease with aging. Avoiding sarcopenia is essential to recovery. Thus, patients should sit up in bed, transfer to a chair, stand, and exercise as much as and as soon as is safe for their surgical and medical condition. Nutritional deficiencies also may contribute to sarcopenia. Thus, nutritional intake of patients on complete bed rest should be optimized. Tube feeding or, rarely, parenteral feeding, may be necessary (102).

2.2.3.3.9. Other issues

Certain types of surgery require additional precautions. For example, hip surgery requires that patients be moved and positioned so that the hip does not dislocate. Any physician moving such patients for any reason, including auscultation the lungs, must know the positioning protocol to avoid doing harm; often, a nurse is the best instructor (102).

DOI:10.14753/SE.2013.1821

3. OBJECTIVES

My aim was to implement the idea of using an additional drug to some types of surgeries to achieve better results, and to help in solving the challenges that face the anesthesiologists in the daily practice by conducting a prospective randomized control trial scheduled for spinal fusion, scoliosis, and microdiscectomy surgery in two different manners:

a. To compare a control group who takes normal saline intra-operatively with remifentanil and propofol to the test group who takes ketamine intra-operatively in spinal fusion and scoliosis surgery.

b. To compare a control group who takes normal saline intra-operatively with remifentanil and propofol to two test groups who takes ketamine post-operatively in addition to intra-operative stage in microdiscectomy surgery.

- To determine if the use of ketamine would give better, intra-operative hemodynamic stability by measuring the heart rate and mean arterial pressure of the patients,
- To determine if the use of ketamine would give better post operative pain control by measuring the visual analogue scale score, and the total morphine consumption.
- To monitor the influence of lowering morphine consumption on the nausea and vomiting side effect.
- To monitor if ketamine low dose induces any regular side effects; which usually occur in the normal dose as hallucination.
- To involve the pharmacist special pharmacodynamic and pharmacological knowledge in the surgery room with the anesthesiologists in order to share in solving the daily challenges which face the anesthesiologists in complicated types of surgeries.
- To add new experience area to the clinical pharmacist, and to involve them in applying new role and duties in the different stages of the surgeries.

DOI:10.14753/SE.2013.1821

4. METHODS

4.1 Study design and methods

In order to investigate the out results of the different anesthetics methods, I applied the hypothesis of randomized control trial for control and test group using normal saline , or using low dose ketamine hydrochloride in 3 different types of surgeries, in two different manners: by comparing a control group with one test group who used ketamine intra-operatively in spinal fusion and scoliosis surgeries, and by comparing a control group with two tests groups whom used ketamine intra-operatively and post operatively in microdiscectomy surgery under pharmaceutical care program.

4.1.1 Spinal fusion surgery

The Human Investigation Section of the Institutional Review Board of the Arab Center Hospital, Amman, Jordan, read, considered and subsequently approved the ethics of this investigation and so gave their formal permission for the spinal fusion surgery study to be carried out.

A prospective, randomized, study during the period Jan 2007 - Jan 2009, was carried out by the same surgical and anesthetic teams in one hospital.

4.1.1.1 Patient selection

All patients were informed about the details of the procedures and a written consent was obtained for each patient. Patients who were studied were scheduled for posterior lumbar and thoracic spinal fusion surgery. In total 30 adult patients were allocated randomly into two equal groups. Control Group (G1), 3 males and 12 females, and test Group (G2), 7 males and 8 females. The age range and weight of the patients in G1 was 49- 58 years old and 68 ± 12 kg respectively, in G2 patients were 53-59 years old, and 66 ± 13 kg (Table 9).

DOI:10.14753/SE.2013.1821

Table 9 The gender, age, body weight, baseline heart rate and mean arterial pressure in the patients (n=30) used in this study

Group	Group 1 (n = 15)	Group 2(n=15)
Male/female	3- 12	7 - 8
Age (years)	49 - 58	53 - 59 NS
Body Weight (kg)	68 ± 12	66 ± 13 NS

Key: NS: Not Significant

4.1.1.2. Chart review for medication selection

All drugs and the used drug doses were accurately counted and documented in the patients' medical charts at the time of administration.

Anesthesia

All patients were given midazolam 0.25 mg/kg orally 30 minutes before surgery as a premedication. On arrival at the operation theatre, the following drugs were given intraoperatively, propofol 2 mg/kg IV bolus was given for induction in both groups followed by propofol infusion at a dose of 6mg/kg/h, atracurium 0.6 mg/kg was given to facilitate orotracheal intubation just at the induction, sevoflurane (1-1.5% v/v) was given in a carrier gas of a 1:1 nitrous oxide: oxygen mixture and anesthesia was pre-induced with remifentanil 1μg/kg in both groups followed by remifentanil infusion at a dose of 0.2 μg/kg/minutes, and placebo infusion of normal saline 0.9% in G1, or followed by a combination of remifentanil infusion in a dose of 0.2 μg/kg/minutes and racemic ketamine (Tekam Al-Hikma, Jordan) infusion at a dose of 1μg/kg/minutes in G2 administered in 2 different cannulas (Table 10).

DOI:10.14753/SE.2013.1821

The lungs were ventilated to maintain a normocapnia with end-tidal carbon dioxide pressure around 35 mmHg using 50% oxygen in air. Continuous arterial pressure monitoring and frequent blood gas assessments provided appropriate data for all patients. Patients received crystalloid with ringer's lactate being intravenously infused at the rate of 10 ml/kg/h. Blood loss was continuously collected and measured using 'gauze and bottle suction technique' where the lost blood was continuously collected and described elsewhere (1). Briefly, the blood was very carefully collected, measured. Its volume was recorded and an equivalent volume of packed red blood cells was replaced. A transfusion for replacement started when the blood loss exceeded 500 ml. In addition, a Foley's catheter connected to a urine bag was inserted in all patients.

Table 10 The medications given for G1 and G2 patients during spinal fusion surgery

Stages of medication admission	Groups of medications	Medication given	G1	G2
I-pre-operative	Sedative	Midazolam G1, G2	Yes	Yes
II-Intra-operatively	Anesthetics:- IV	Propofol Ketamine	Yes No	Yes Yes
	Anesthetics:- inhaler	Sevoflurane	Yes	yes
	Analgesics	Remifentanil	Yes	yes
	Muscle relaxants	Atracurium	Yes	Yes
	Antidote	Neostigmine Atropine	Yes Yes	Yes Yes
III- Postoperatively	Analgesics	Morphine	Yes	Yes

Key: Yes: used No : not used

DOI:10.14753/SE.2013.1821

At the end of the operation all drugs were stopped, both groups received antidotes which were - neostigmine (2.5 mg/IV), atropine (1 mg/IV) and they were administered together in a single bolus dose from one syringe followed by 100% oxygen (Table 10).

4.1.1.3. Post-operative analgesic administration

The severity of postoperative pain was assessed during the first 24 hours after the surgery by means of the visual faces rating scale and pain was controlled by IV morphine. The morphine infusion pump was set to deliver morphine solution (1 mg/ ml) at rate 3-5 mg / hr in the PACU.

4.1.1.4. Quantitative measurements made during the operation

To ensure the data was collected independently from the clinical pharmacist who organized the study or any health professional members who were aware of the protocol, all the data were collected by pharmacy students, who had received very specific tuition but who were blind and not aware of the contents of the solutions which were at all times under the supervision of highly trained research technicians and nurses.

Heart rate (beats/min), mean arterial pressure (MAP) (mmHg) was recorded at 5-minute intervals during surgery where the dose of the infused drugs was adjusted to keep the mean blood pressure around 60 mmHg. The duration of anesthesia and the total time of the surgery (min), the volume of blood loss (ml) and urine output (ml) and the immediate recovery time were recorded. The early pain perception was measured by the time (min) that passed between extubation and the first request for a dose of analgesic. The total consumption of morphine (mg) over the first 24 hours postoperatively was measured. Finally anesthetic-related complications, including nausea, vomiting, pruritus, dysphoria, vision loss, shivering and respiratory depression, were recorded and managed accordingly.

DOI:10.14753/SE.2013.1821

4.1.2. Scoliosis surgery

The Human Investigation section of the Institutional Review Board of the Arab Center Hospital, Amman, Jordan, read, considered and subsequently approved the ethics of this investigation and so gave their formal permission for the scoliosis surgery study to be carried out. A prospective randomized study in a period from Jan 2007 - Jan 2009 was carried out by the same surgical and anesthetic teams in one hospital.

4.1.2.1. Patient selection

All patients were informed about the details of the procedures and their written consent was observed for each patient. All the patients included in this study were undergoing scoliosis surgery for the first time with a curvature of the spine greater than 40°. I studied 40 adult patients allocated randomly into two equal groups, control Group (G1), and test Group (G2) (Table 11).

Table 11 The gender, age, body weight, baseline heart rate and mean arterial pressure in the patients (n=40) used in this study

Group	Group 1 (n = 20)	Group 2 (n = 20)
Male- female	8 - 12	7 – 13
Age (years)	19 - 23	20- 24 NS
Body Weight (kg)	54 ± 13	55 ± 15 NS
Baseline Heart Rate value (beats per minute)	80 ± 2	83 ± 4 NS
Baseline MAP value (mmHg)	90 ± 3	93 ± 2 NS

Key: NS: Not Significant

DOI:10.14753/SE.2013.1821

4.1.2.2. Chart review for medication selection

All drugs and drug doses were counted and documented in medical charts so as to ensure accurate observations were recorded.

4.1.2.2.1. Anesthesia

All patients were given oral midazolam 0.25 mg/kg 30 minutes before surgery as a premedication. On arrival at the operation theatre, the following drugs were given intraoperatively, propofol 2 mg/kg IV bolus was given for induction in both groups followed by propofol infusion in a dose of 6 mg/kg/h, atracurium 0.6 mg/kg was given to facilitate orotracheal intubation just at the induction, sevoflurane (1-1.5% V/V)was given in a carrier gas of a 1:1 nitrous oxide: oxygen mixture and a bolus dose of 11μg/kg of remifentanil was given at the induction for both groups followed by remifentanil infusion in a dose of 0.2 μg/kg/minutes in G1, or followed by a combination of remifentanil infusion in a dose of 0.2 μg/kg/minutes and ketamine infusion in a dose of 1μg/kg/minutes in G2 administered in 2 different cannulas (Table 12).

The lungs were ventilated to maintain a normocapnia with end-tidal carbon dioxide pressure around 35 mmHg using 50% oxygen in air. Continuous arterial pressure monitoring and frequent blood gas assessments provided appropriate data for all patients.

Patients received crystalloid + Ringer's lactate was IV infused fluid at rate of 10 ml/kg/h. Blood loss was continuously collected and measured using a gauze and bottle suction technique which has been described elsewhere (1). Briefly, the blood was very carefully collected, measured, its volume recorded and an equivalent volume of packed red blood cells was replaced. A transfusion for replacement started when the blood loss exceeded 500 ml. In addition a Foley's catheter, connected to a urine bag was inserted in all patients.

DOI:10.14753/SE.2013.1821

Table 12 The medications given for G1 and G2 patients during scoliosis surgery

Stages of medication admission	Groups of medications	Medication given	G1	G2
I- pre-operative	Sedative	Midazolam G1, G2	Yes	Yes
II- Intra-operatively	Anesthetics:- IV	Propofol Ketamine	Yes No	Yes Yes
	Anesthetics:- inhaler	Sevoflurane	Yes	Yes
	Analgesics	Remifentanil	Yes	Yes
	Muscle relaxants	Atracurium	Yes	Yes
	Antidote	Neostigmine Atropine	Yes Yes	Yes Yes
III- Postoperatively	Analgesics	Morphine	Yes	Yes

Key: Yes: used
No : not used

4.1.2.3. Wake up test

The Wake up test was measured using the procedure described earlier (29). Essentially, the duration of the onset and regression time of sensory motor blockade are assessed in this wake-up test by asking the patients to move their fingers and their toes. It is a precautionary test done to assess any possible damage to the spinal cord caused by the surgical technique and placement of the correction devices.

In order to carry out the wake up test all the drugs were stopped, antidotes were given including; neostigmine (2.5 mg/IV) and atropine (1mg/IV) which were administered together in a single bolus dose from one syringe (10).

DOI:10.14753/SE.2013.1821

When the wake up test was completed, when the patients responded to the first verbal commands; they were then re-anesthetized with the same induction drugs in doses identical to those used originally.

During the operation for the purposes of maintenance the patients in Groups 1 and 2 received their respective drugs. At the end of the operation both groups received doses of neostigmine, atropine as described above along with 100% oxygen. Approximately 15 min before the end of surgery, a 1–2 μg/kg dose of fentanyl IV was given intraoperatively for patients (103), after their recovery but before being transferred to the recovery room, in order to ensure that no spinal injury had occurred.

4.1.2.4. Post-operative analgesic administration

The severity of postoperative pain was assessed during the first day after surgery by means of visual faces rating scale and pain was controlled by IV morphine. The morphine infusion pump was set to deliver morphine solution (1 mg/ ml) at rate 3-5 mg / hr in the (PACU).

4.1.2.5. Quantitative Measurements made during the operation

To ensure the data was collected independently from me, all the data were collected by very carefully prepared pharmacy students who were blind and not aware of the contents of the solutions and who acted in this role under the supervision of highly trained research technicians and nurses.

Heart rate (beats/min), mean arterial pressure (MAP) (mmHg) was recorded at 5 minute intervals during surgery where the dose of the infused drugs was adjusted to keep the mean blood pressure around 60 mmHg. The duration of anesthesia and the total time of the surgery (min), the volume of blood loss (ml) and urine output (ml), the time to achieve the wake up test and the immediate recovery time were recorded. The early pain perception

DOI:10.14753/SE.2013.1821

was measured by the time (min) that passed between extubation and the first request for an analgesia dose. Total consumption of morphine (mg) over the first 24 hours postoperatively was measured. Finally potential anesthetic-related complications, including nausea, vomiting, pruritus, dysphoria, vision loss, shivering and respiratory depression, were found, recorded and managed accordingly.

4.1.3. Microdiscectomy surgery

All patients were treated by the same surgical anesthetic and nursing teams and all were scheduled for lumbar microdiscectomy surgery using the same operative procedures.

The Human Investigation Section of the Institutional Review Board of the Hospital read considered and subsequently approved the ethics of this investigation and so gave their formal permission for this study to be carried out. All patients were informed about the details of the procedures and written consent was obtained from each patient.

4.1.3.1. Patient selection

Forty-five patients scheduled for lumber microdiscectomy surgery were prospectively randomized under double-blind conditions to one of three groups of 15 patients: Control Group (G1) received normal saline; Group 2 (G2) received intra-operative ketamine (1μg/kg/min) and Group 3 (G3) received intra-operatively and post-operatively ketamine (1μg/kg/min) for the first 24 h after surgery.

Inclusion criteria were that the patient was adult who had a level of education which enabled them to understand the use of the patient controlled analgesia technique. Those patients who had used bed rest and had physical therapy sessions by licensed physical therapist to relieve their lower back pain at least 48 h prior to surgery were included in the trial.

Exclusion criteria were that patients with severe back pain who were receiving chronic narcotic analgesics treatment were excluded, as were patients with major systemic diseases.

Details of patient gender, age, and body weight for the 3 groups are shown in Table 13.

Table 13 Gender, age, body weight in the 3 groups of patients studied

Variable	Group 1 (n=15)	Group 2(n=15)	Group 3(n=15)
Gender*	8-7	7-8	6-9
Age(years)	51 ± 2.5	55 ± 2.5	55 ± 2.6
Body weight (kg)	7 1± 2.6	69 ± 2.6	70 ± 2.3

Notes:* Gender is displayed as a ratio of male to female. Values are presented as the mean ± standard deviation or number. There were no significant differences between three groups.

4.1.3.2. Chart review for medication selection

All drugs and used drug doses were counted and documented in medical charts so as to ensure accurate observations were recorded.

4.1.3.2.1. Anesthesia

All patients were given midazolam 0.25 mg/kg orally, 30 minutes before surgery as a premedication. On arrival at the operating theatre, the following drugs were given: Propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1-1.5% V/V) in a carrier gas mixture of 1:1 nitrous oxide : oxygen was used for all patients.

DOI:10.14753/SE.2013.1821

Anesthesia was pre-induced using remifentanil 1μg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 μg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 μg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 μg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 μg/kg/min for 24h (Table 14).

Table 14 The medications given for G1, G2, and G3 patients during microdiscectomy surgery

Stages of medication admission	Groups of medications	Medication given	G1	G2	G3
I-pre-operative	Sedative	Midazolam G1, G2	Yes	Yes	Yes
II-Intra-operatively	Anesthetics:- IV	Propofol Ketamine	Yes No	Yes Yes	Yes Yes
	Anesthetics:- inhaler	Sevoflurane	Yes	Yes	Yes
	Analgesics	Remifentanil	Yes	Yes	Yes
	Muscle relaxants	Atracurium	Yes	Yes	Yes
	Antidote	Neostigmine Atropine	Yes Yes	Yes Yes	Yes Yes
III- Postoperativly	Analgesics	Morphine Ketamine	Yes No	Yes No	Yes Yes

Key: Yes: used
No : not used

DOI:10.14753/SE.2013.1821

4.1.3.3. Post operative analgesic administration

The severity of postoperative pain was assessed during the first 24 hours after surgery by means of the visual analog scale score (VAS), identifying 0 as no pain and 100 the worst imaginable pain. When the (VAS) score was ≥ 40, IV morphine was given until the (VAS) score was ≤ 40 for all three groups. The morphine infusion pump was set to deliver the morphine solution (1 mg/ ml) at a rate of 3mg per demand in the PACU for all three groups. Group 3 received an additional infusion of ketamine 1μg/kg/min for 24 hours, whereas the other two groups (G1, G2) simply received the placebo – 0.9% normal saline.

4.1.3.4. Quantitative measurements made during the operation

Collecting the data was carried out independently from the clinical pharmacist who organized the study or from physicians who were cognizant of the protocol. The anesthesiologist technicians assist the anesthesia team in the patient monitoring, where they collected all the data blindly.

The duration of surgery (min), the time taken from intubation to extubation was record for each patient and expressed as the duration of the operation.

Early pain perception was measured by the time (min) that passed between extubation and the first request for a dose of analgesic. The total consumption of morphine (mg) and numeric rating scale were monitored at 6, 12 and 24 h postoperatively.

Anesthetic-related complications such as dysphoria or hallucination were recorded when present. Nausea and vomiting were recorded by using by using a three response scoring system: none, mild nausea, severe nausea and vomiting. The complications were managed according to each individual case.

DOI:10.14753/SE.2013.1821

4.2. Summary to the inclusion and exclusion criteria for patients undergoing the three types of surgeries

Summary of the inclusion and exclusion criteria for spinal fusion, scoliosis, and microdiscectomy surgeries can be seen in table 15

Table 15 Summary of the inclusion and exclusion criteria for spinal fusion, scoliosis, and microdiscectomy surgeries

	Spinal fusion	**Scoliosis**	**Microdiscectomy**
Number of patients	30	40	45
Gender: M- F	G1 (3-12) G2 (7- 8)	G1 (8- 12) G2 (7- 13)	G1 (8-7) G2(7-8) G3(6-9)
Age	49-59	19-24	49-58
Area of surgery	Lumber and thoracic	More than 40 degree curvature	Lumber
Level of education	Acceptable	Acceptable	Acceptable
Narcotic addiction	No	No	No

4.3. Data analysis

On completion of the ‘field work’, coded data were examined by using the Statistical Package for Social Sciences (SPSS/PC+) program, version 19. All data entries were double checked to ensure accurate data entries.

DOI:10.14753/SE.2013.1821

In spinal fusion and scoliosis surgeries data were expressed as mean ± 2SD and were analyzed using Chi square test for categorical comparisons for the existing or none exciting of pain, while Student's t test was applied for the rest of variance for two groups' methods. P value <0.05 was considered significant.

In microdiscectomy the sample size estimation was based on a power calcultion showing that 15 patients per group were necessary to achieve 80% power for detecting a 20% difference in the different variables between group 1 with groups 2 and 3 with $\alpha = 0.05$. Data are presented as the mean ± standard deviation or as numbers. Differences among group means were compared using one-way analysis of variance and post hoc comparisons at various points in time using Bonferroni's type I error rate correction for multiple tests of significance. Gender and complication rates were analyzed by pearson's Chi- square test. $P < 0.05$ was considered to ba statistically siginificant.

Null hypothesis: Ketamine has no effect on hemodynamic stability, and total morphine consumption.

4.4. Introducing the pharmaceutical care program

4.4.1. Pharmaceutical care program

Together on the basis of my pharmacology knowledge and the experience of the anesthesiologist, I applied the idea of using the multi character of keamine in different surgeries to achieve better outcome.

In my study a clinical pharmacist performed many activities for the patients pre-operatively, during, and after different surgeries.

1) I had a pivotal educational role in different stages of the surgery and before the operation to allay patients' fears and apprehensions and to minimize the consequences of this very painful surgical experience.(During the wake up test in scoliosis surgery (29), the duration of onset and reversal of the motor blocks in order to avoid possible damage to the spinal cord).

2) Checking the patients' health condition and wellbeing pre-operatively.

3) All medication consumption was monitored for two weeks prior to the surgery specifically for those drugs which are known to have an effect on blood clotting.

4) I also checked the storage instructions and expiry date for all drugs before they were used.

5) I provided the patients with simple information about the disease and drug therapy pre-, intra- and postoperatively during their hospital stay.

6) I set up a scheme which ensured that plans were in place for all medications used, to avoid errors and for the documentation.

7) I scheduled a plan for collecting the data independently.

8) To ensure that patients received adequate morphine dose as a postoperative analgesic whenever it was required following their operation, on the evening before surgery, they were instructed how to use the visual faces rating scale for scoliosis , spinal fusion, and microdiscectomy surgery.

During this instruction, patients were asked to point to various facial expressions ranging from a smiling face (no pain) to an extremely unhappy one that expresses the worst possible pain (104) Figure 1.

DOI:10.14753/SE.2013.1821

Figure 1 - Expresses the degree of pain according to face expression

To use this scale, your doctor should explain that each face shows how a person in pain is feeling.

- **Face 0** is very happy because he or she doesn't hurt at all.
- **Face 1** hurts just a little bit.
- **Face 2** hurts a little more.
- **Face 3** hurts even more.
- **Face 4** hurts a whole lot.
- **Face 5** hurts as much as you can imagine, although you don't have to be crying to feel this bad.

I considered the degree of pain as; no pain (face 0) and pain (face 1, 2, 3, 4, 5).

9) The severity of postoperative pain was assessed during the first 24 hours of the surgery. In spinal fusion and microdiscectomy surgery patients were chosen to have a level of education which enabled them to understand the use of the patient controlled analgesia technique.

10) To involve the pharmacists special pharmacodynamic knowledge in the surgery room to the anesthesiologists, and to give advices concerning combining drugs together to have better achievements.

11) Finally I recorded all the details of the potential drug allergic responses and major side effects if exist.

DOI:10.14753/SE.2013.1821

5. RESULTS

5.1. The out results of investigating the influence of adding ketamine in 3 types of surgery intra- and post- operatively by applying pharmaceutical care program

5.1.1. Spinal fusion surgery

5.1.1.1. Patient characteristics

The two groups studied were comparable as regards sex, age, weight, duration of surgery and anesthesia.

The analysis showed that there were no significant differences between the number of males and females in their respective groups and also for comparisons made between G1 and G2 in respect of their ages, and body weight. In the absence of any significant differences being found they were subsequently considered as one group despite their apparent gender and age differences.

After the pre-operative tests, patients were found to be free of any major systemic disease such as coronary heart disease or hypertension and they were fit to be operated upon according to the criteria used by the anesthesiologists involved in this study.

5.1.1.2. Intra operative and Post-surgical analysis

The HR was 67 ± 4 beats per minute for G1 and 70 ± 1 beats per min for G2, while MAP was 60 ± 2 mmHg for G1 and 66 ± 5 mmHg for G2, These results are significantly lower ($p < 0.05$) in G1 than in G2 (Table 14). However there were no significant differences between the two groups regarding blood loss which was 1800 ± 50.6 ml for G1, and1833 ± 80.1 ml for G2. Also there were no differences in the urine flow which was 350± 3 ml for G1 and 337± 6 ml for G2. The mean operation time was 242.1 ± 3.3 min for G1 and 238.4

DOI:10.14753/SE.2013.1821

± 3.6 min for G2, and duration of anesthesia was 273.6 ± 5.3 min for G1 and 266.7 ± 3.5 min for G2 (Table 16). Neither of which were significantly different.

Table 16 Clinical measurements made during spinal fusion surgery for G1 and G2

	G1	**G2**
Heart Rate (beats per min)	67 ± 4	70 ± 1*
MAP (mmHg)	60 ± 2	66 ± 5*
Total blood loss (ml)	1800 ± 50.6	1833 ± 80.1 NS
Total urine output (ml)	350 ± 3	337 ± 6 NS
Duration of surgery (min)	242.1 ± 3.3	238.4 ± 3.6 NS
Duration of anesthesia (min)	273.6 ± 5.3	266.7 ± 3.5 NS

Key:*Signifies p< 0.05, NS: Not significant, data are expressed as the mean ± 2SD

The immediate recovery time was 3.3 ± 2.6 min for G1 and 7.1 ± 2.8 min for G2, and the time which went past to the first patient's analgesia request in PACU was 19.5 ± 3.2 min for G1, and 22.9 ± 3.5 min for G2; these results were significantly greater ($p < 0.05$) in G2 as compared with G1 (Table 17).

DOI:10.14753/SE.2013.1821

Table 17 Differences in pain score between G1 and G2

Number of Patients with:	G1	G2	No.	Statistics
No Pain	2	10	G1+ G2 12	
With Pain	13	5	G1+ G2 18	p <0.05
Total Number	15	15	Total 30	

In G1, two patients had no pain, while 13 patients complained of different degrees of pain. In contrast, 10 patients from G2 had no pain, while just 5 of them complained of different degrees of pain (Table 16). For G1, the dose needed for patients to ask for morphine was 60±10 mg, as compared with G2 patients who had a mean dose of 45±5 mg. This result was significantly different ($p< 0.05$) during the first 24 hours after surgery as compared with G1 (Table 18).

Table 18 Post-surgical analysis for G1 and G2

	Group 1 (n = 15)	Group 2 (n = 15)
Immediate recovery time (min)	3.3 ± 2.6	7.1 ± 2.8 *****
Time to first patient analgesia dose request in PACU (min)	19.5 ± 3.2	22.9 ± 3.5*****
Needed dose of morphine (mg)	60±10	45±5*****

Key: * Signifies $p< 0.05$, data are mean ± SD.

DOI:10.14753/SE.2013.1821

5.1.1.3. Potential for drug allergic responses and adverse effects

No patients in either group reported dysphoria or hallucination, shivering and respiratory or visual loss but no differences were noted in the incidence of purities and postoperative nausea and vomiting in the two groups.

5.1.2. Scoliosis surgery

5.1.2.1. Patient characteristic

The two groups studied were comparable as regards age, weight, and sex.

Preliminary analysis showed that there were no significant differences between males and females in their respective groups for any of the parameters measured and so, they were subsequently considered as one group despite their gender and age differences, perhaps indicating the success of the initial randomization process (Table 11).

5.1.2.2. Intra operative and Post-surgical analysis

The HR and MAP was significantly lower ($p < 0.05$) in G1 than in G2 (Table 19). However, there were no significant differences between the two groups regarding blood loss, urine flow, wake up test, mean operative time and duration of anesthesia (Table 19).

DOI:10.14753/SE.2013.1821

Table 19 Clinical measurements (Mean± 2SD) made during scoliosis surgery for G1 and G2 groups of patients

	G1	G2
Heart Rate (beats per minute)	67 ± 4	70 ± 2*
MAP (mmHg)	60 ± 3	70 ± 5*
Time needed for wake up test (min)	13 ± 1.3	14 ± 1.2 NS
Total blood loss (ml)	1800 ± 51	1833 ± 80 NS
Total urine output (ml)	350 ± 3	338 ± 6 NS
Duration of surgery (min)	240 ± 3	239 ± 4 NS
Duration of anesthesia (min)	272 ± 5	267 ± 4 NS

Key: *Signifies P< 0.05, NS: Not Significant

Concerning the immediate recovery time and the time which passed until the first patient analgesia request in the PACU, the recorded values were significantly different. A value of $p < 0.05$ was found when G2 were compared to G1 (Table 20).

There was significant difference between the two groups as G 2 patients also consumed 25% less morphine than G1 patients, which on analysis was found to have a value of $p< 0.05$ (Table 20).

DOI:10.14753/SE.2013.1821

Table 20 Post surgical analysis for patients (n=40) for their immediate recovery time, time to first request for analgesia and total morphine consumption in G1 and G2. All values are mean ± 2SD

	Group I (n = 20)	**Group II (n = 20)**
Immediate recovery time (min)	3.3 ± 2.6	7.1 ± 2.9 *****
Time to first patient analgesia dose request in PACU (min)	19.5 ± 3.2	22.9 ± 3.6*****
Total 24 hr morphine consumption (mg)	60 ± 10	45 ± 5*****

Key: * Signifies P< 0.05

5.1.2.3. Potential for drug allergic responses and adverse effects

No patients in either group reported dysphoria, shivering and respiratory or visual loss and no differences were noted in the incidence of pruritus, postoperative nausea and vomiting in the two groups.

5.1.3. Microdiscectomy surgery

Statistical data from the Arab Center Hospital, Amman, Jordan showed that the average number of lumbar laminectomy operations per year was 60. Consequently this study reflects the findings from 25% of this surgery carried out by the surgical and anesthetic team in each year of the study. Not all the patients could be included in the study due to their exclusion by the exclusion criteria which were used.

DOI:10.14753/SE.2013.1821

5.1.3.1. Patient characteristics

The three groups of patients studied were found to be comparable as regards sex, age, weight, and the duration of the surgery (Table 13). Comparisons of the data found that there were no significant differences (P>0.05) between any of the parameters measured across the groups. There were no significant differences between the number of males and females in their respective groups and also for comparisons made between G1, G2 and G3 for their ages, and body weight. In the absence of any significant differences being found between the groups they were subsequently considered as comparable groups despite their apparent gender and age differences (Table 13).

After the pre-operative tests, patients were found to be free of any major systemic disease such as coronary heart disease and/or hypertension and they were considered fit to be operated upon according to the usual criteria used by the anesthesiologists involved in this study. The drug history of each patient taken by the pharmacists did not show any major differences between individuals in the three groups and so were all considered suitable for the trial.

5.1.3.2. Analysis of the duration of the surgical procedure

The duration of the surgery was not significantly different between the patients in the three groups (P > 0.05) (Table 21).

5.1.3.3. Time for the first request for analgesia in the PACU

The time to the first patient's analgesia request in PACU was 17 ± 1.7 min for G1, 23.60 ± 1.8 min for G2 and 23.9 ± 1.83 min for G3. The results of the statistical comparisons show that there was a significant difference between the results of G1 and G2 (P > 0.05), and between the results of G1 and G3 (P > 0.05), whilst there was no significant difference between G2 and G3 (Table 21).

DOI:10.14753/SE.2013.1821

Table 21 Duration of surgery (min), and the time (min) for the first request for analgesia in the PACU

	Group1 (n=15)	**Group 2 (n=15)**	**Group 3 (n=15)**
Duration of surgery (min)	61 ± 2.80	60 ± 2.90	61± 1.1 NS
Time for first patient analgesia request in PACU (min)	17± 1.7	23.60±1.80*	23.9±1.83*

Notes: NS: Not significant, data are expressed as the mean ± SD *P< 0.05 versus group 1

5.1.3.4. Dosage of morphine requested at 6, 12 and 24 hours after surgery

All the comparisons made established that the three groups were significant different from each other for morphine dose 6, 12, and 24 hr after the surgery, the cumulative morphine dose was significantly the lowest for G3 (P <0.05), while the doses required for those patients not treated with a continuous infusion of ketamine were significantly greater than when it was present. These results are shown in Table 22.

DOI:10.14753/SE.2013.1821

Table 22 Cumulative requested doses of morphine for the 6, 12 and 24 hours post-operative period

	Group1 (n=15)	Group2 (n=15)	Group 3 (n=15)
6h dose (mg)	9 ±2.30	6.8±2.65*	3±2.26*,†
12h dose (mg)	21±2.65	16.2±2.73*	9.2±2.11*,†
24h dose (mg)	60±2.60	45.3±3.26*	26.9±2.71*,†

Notes: Data are presented as the mean ± standard deviation

*P<0.05 versus group 1; †P < 0.05 versus group 2

5.1.3.5. Results from the (VAS) of patients' perception of pain

The visual analog scale score (VAS) results for the perception of pain were measured at 6, 12, and 24 hr after surgery and are shown in Table 23. All the comparisons made established that the three groups were significant different from each other; where G3 was significantly the lowest and G1 was the highest (P <0.05).

Table 23 VAS score assessments after 6, 12, and 24 hours

Group	Group1 (n=15)	Group 2 (n=15)	Group 3 (n=15)
VAS 6	44.00±5.071	36.0±5.0*	27.3±4.5*,†
VAS 12	58.00±6.761	50.7±4.5*	40.0±3.8*,†
VAS 24	56.00±5.071	44.7±5.2*	35.3±5.2*,†

Notes: Data are presented as the mean ± standard deviation

*P<0.05 versus group 1; †P< 0.05 versus group 2

DOI:10.14753/SE.2013.1821

5.1.3.6. Drug side effects

No transient psychotic events e.g. hallucinations were reported for any of the groups including the ketamine group at any of the time points measured. Nausea and vomiting were the main drug induced side effects observed over the first 24 hr. post-operative period (Table 24). All the comparisons made established that the three groups were significant different from each other; where G3 patients had the lowest side effect versus G2 and G1, where G1 had the highest score ($P < 0.05$).

Table 24 Nausea and vomiting over the first 24 hr. post-operative period

Nausea and vomiting Status	Group 1 (n = 15)	Group 2 (n = 15)	Group 3 (n = 15)	Statistic
No	7	10	14	P< 0.05
Yes	8	5	1	P< 0.05

Values are presented as numbers

DOI:10.14753/SE.2013.1821

6. DISCUSSION

6.1. The influence of adding ketamine in spinal fusion, scoliosis, and microdiscectomy surgery intra operatively, and post operatively by applying pharmaceutical care program

6.1.1. Spinal fusion surgery and scoliosis surgery

Hemodynamically, the HR and MAP were significantly lower in G1 than in G 2. Several studies are in agreement with this study results which have previously shown that remifentanil causes arterial hypotension and bradycardia with IV anesthetic agents or general anesthetics (1, 49, 50).

In G 2, I chose to use a low constant dose of ketamine because this lower dose would lead to less tachycardia and hypertension and a shorter duration of action, potentially resulting in a lowered incidence of ketamine side effects such as, postoperative hallucinations and emergence delirium. The finding that the HR and MAP did not decrease below the normal values is possibly due to the previous reports where catecholamine release by ketamine, has been reported to cause both tachycardia and hypertension (51,52) an action that would attenuate the action of remifentanil.

I found no significant difference between the two groups regarding blood loss and urine flow and the finding that both groups had adequate urine output is possibly due to the very careful fluids and replacement therapy carried out during the surgical procedure.

As regards to recovery from anesthesia, I found that patients in G1 recovered quicker than those given the ketamine-remifentanil-propofol technique in G2. These results are perhaps due to the short terminal plasma half-life, 3-5 minutes of remifentanil (14) the presence of an ester side chain allows remifentanil to be rapidly broken down by non-specific esterases to nearly inactive metabolites, so recovery from an intraoperative infusion can be rapid (8). In contrast, in G2, the long elimination half-life of ketamine (2.3 ± 0.5 hours) delays the patients' recovery (15).

DOI:10.14753/SE.2013.1821

The time to first patient controlled analgesia dose request in PACU (Early pain perception), was significantly less in GI. This could be due to the hyperalgesia of surgical injury and the development of opioid-induced tolerance related to remifentanil infusions. Both involve activation of N-methyl-D-asparate (NMDA) receptors in CNS, and subsequent biochemical processes resulting in centeral sensitization, increase spinal dynorphin activity and the activation of intracellular protein kinase (4). Sharing of NMDA receptor activation by both processes suggests that ketamine, an NMDA receptor antagonist, in ketamine-remifentanil group may substantially enhance opiate-induced antinociception (53).

Frederic Adame and colleagues (54) evaluated the effect of ketamine in a dose of 1.5μg/kg/min for post-operative pain relief and the total morphine consumption after total knee artheroplasty. Their results confirm that ketamine is a useful analgesic adjuvant in perioperative multimodal analgesia with a positive impact on early knee mobilization, and that their patients required significantly less morphine than control group.

Continuous intraoperative ketamine-remifentanil combined infusions G2, when compared to continuous remifentanil infusion alone G1, the postoperative pain scores and total morphine consumption were significantly less in G2. Ketamine may produce ant nociception through interaction with spinal mu receptor, NMDA receptor antagonism, and activation of the descending pain inhibitory monoaminergic pathways (55), which is expressed by alpha2-adrenoceptors at the spinal level (56). Analgesia produced in humans by systemic ketamine up to 0.3 mg/kg is not reversed (105), which suggests that the analgesic effect of ketamine is mediated by a non-opioid mechanism, possibly involving phencyclohexyl piperidine receptor-mediated blockade of the NMDA-receptor-operated ion channel.

Even though a smaller ketamine dose was used in this study, it produced a significant decrease in postoperative pain scores and morphine consumption. The affinity of ketamine for NMDA receptors has been shown to be more than an order of magnitude higher than that for mu receptor (57) and several-fold higher than that for monoamine transporter sites or other non-NMDA receptors (i.e., acetylcholinesterase and the epsilon receptor (58),

DOI:10.14753/SE.2013.1821

which suggests that the smaller the dose, the more selective is the ketamine interaction with NMDA receptors. Ossipov and his colleagues showed that analgesia produced by the systemic coadministration of an opiate and an α2-adrenoceptor agonist, for example clonidine or meditonidine are synergistic (59).

In agreement with my results, Stubhaug et al. showed that a low-dose IV infusion of ketamine during and after surgery reduces mechanical punctuate hyperalgesia surrounding the surgical incision. These indicate that blockade of NMDA receptors prevents the central sensitization caused by nociceptive input during and after surgery (106) other studies have demonstrated that ketamine in combination with morphine provides superior postsurgical pain relief at lower dosage and with fewer side effects than morphine alone (107).

These results demonstrate that the combination of low dose ketamine and remifentanil infusions as TIVA during spinal fusion and scoliosis surgery may provide better hemodynamic stability, so satisfying a major surgical requirement.

Adding low dose ketamine hydrochloride infusion can be applied as a routine therapy to improve the hemodynamic stability during spinal fusion and scoliosis surgery and reduce the postoperative morphine consumption.

6.1.2. Microdiscectomy surgery

I have examined the use of low dose ketamine in both intra- and post - operative lumbar microdiscectomy surgery because it is well known that patients undergoing this type of surgery experience severe pain in the postoperative period (108).

Fountas et al (1999) have examined different methods for postoperative pain after lumbar microdiscectomy surgery (23) but have not used a low dose of ketamine, such as 1 μg /kg/min as used in this study, as a possible method for such control.

The dual effect of ketamine of being a good analgesic at sub-anaesthetic doses and a mechanism of action mediated primarily by a non-competitive antagonism at N-methyl-D-

aspartic acid (NMDA) receptors (109) makes this drug a somewhat unusual analgesic. However this unusual analgesic action is well documented as is its ability at low-doses to induce a morphine-sparing effect, which can be a very useful effect to utilize postoperatively (5), and for this reason I have chosen low-dose ketamine in this study. Furthermore, the low dose of ketamine would lead to less tachycardia, hypertension and a shorter duration of action, which potentially would result in a lower incidence of ketamine side effects such as postoperative hallucinations and emergence delirium (106).

Low-dose ketamine (1 μg/kg/min) was previously tested intra-operatively in back surgeries including scoliosis and spinal fusion surgery as a randomized placebo-controlled two groups study. (109, 110) In this study I randomly tested controlled group G1, with G2 patients who used ketamine intra-operatively, and G3 who used ketamine intra and post-operatively in laminectomy surgery.

In this study the time needed to the first request of analgesia in PACU was significantly less ($P < 0.05$) in the groups who received ketamine, either intraoperatively or both intra and post-operatively (G2, G3), rather than those who didn't received ketamine (G1). These results were similar to those reported by Hadi et al (2010) who tested ketamine intraoperatively during spinal fusion surgery (110). However the present study showed that adding ketamine either intraoperatively or both intra and post operatively did not show a significant difference for the time to the first request of analgesia. Both groups (G2, G3) receiving the same dose of ketamine until the end of operation and due to the half-life of the drug it would still have pharmacologically active concentrations in the blood stream for some time afterwards hence giving them some analgesic and morphine -sparing effects.

It is interesting to note that continuous intra-operative ketamine-remifentanil combined infusions (G2) and (G3), when compared with continuous remifentanil infusion alone (G1), resulted in less postoperative pain scores and total morphine consumption in G2 and G3. These results were similar to Hadi et al (2010)(110). On the other hand, intra and post-operative ketamine-morphine infusions (G3), when compared with continuous morphine infusion alone (G2), resulted in lower postoperative pain scores and total morphine

consumption in G3. Similar results were previously reported by Zakine et al. (2008) (8) who carried out an investigation by using the same method of drug administration in another type of surgery.

I used the visual analog scale score (VAS) for the assessment of pain as Kundra et al. (1997) evaluated this method, and recommended using it (111). Consequently this technique of recording pain scores for this type of surgery proved to be useful and discriminatory. Two other studies have demonstrated that ketamine in combination with morphine provides superior postsurgical pain relief at a lower morphine dose, with a lower (VAS) score, and fewer side effects than morphine alone (107,112). These results were similar to mine as our results showed that lowering morphine consumption is associated with reducing its side effects such as nausea and vomiting, and the use of the low dose (1μg/kg/min) of ketamine was not associated with any transient psychotic effects. These results were also confirmed in a previously reported study **(**113,114).

This is not the first study in which ketamine has been used at a low concentration post-surgery as Frederic Adame and his colleagues (115) evaluated the effect of low-dose ketamine on post-operative pain relief and the total morphine consumption after total knee artheroplasty, but ketamine was never tested in microdiscectomy surgery. Their results confirmed that low-dose ketamine was a useful analgesic adjuvant in perioperative multimodal analgesia with a positive impact on early knee mobilization. Their patients required significantly less morphine than the control group. These results were similar to mine. In a further meta-analysis study by Bell et al (16), it was observed that in the first 24 hours after surgery, ketamine reduced postoperative nausea and vomiting which could have been due to a morphine-sparing effect. The problem with this study is that it could not be translated into any specific administration regimen with ketamine and so the present study establishes a safe and effective concentration to use. The present study, by establishing a statistically significant difference between the 3 groups (G1, G2, and G3) for morphine induced nausea and vomiting side effects clearly showed the effectiveness of ketamine to counter such effects.

DOI:10.14753/SE.2013.1821

In this study I have examined different parameters concerning adding low dose ketamine intra and post operatively, other studies have tested further positive impacts of ketamine, on narcotic tolerance patients (53), the achievements of hemodynamic stability(110) and its prevention of post-operative hyperalgesia effect (116), all these parameters give ketamine a superior impact over other analgesics.

6.2. Clinical pharmacists involvement with the study

All previous studies have shown high positive impact of clinical pharmacists on the patients in the different fields (24).

In this study I have applied uniquely a full pharmaceutical care program in different surgeries, where up to my best knowledge; this is a new field for the clinical pharmacist.

I was trained to follow all the renowned procedure of the surgery together with the physicians (98-100). I have applied the major duties of the clinical pharmacist, starting pre-operatively by: physical preparation (99).

After the pre-operative tests, patients were found to be free of any major systemic disease such as coronary heart disease or hypertension and they were fit to be operated upon according to the criteria used by the anesthesiologists involved in this study.

Patients are often fearful or anxious about having surgery. I have applied the psychological preparation (96, 101, 104) to allay patients' fears and apprehensions and to attempt to minimize the consequences of this very stressful surgical experience.

Postoperative pain care was fulfilled in the evening, before the operation, patients were instructed how to use the - 100 visual analog scale score (VAS) for microdiscectomy (86).

I set up a scheme to fulfill the rest of the clinical pharmacists' duties, (86, 98) which ensured that plans were in place for all medications used, to avoid errors and for the documentation.

DOI:10.14753/SE.2013.1821

As other previous studies did post-operatively (100); in this study patients were moved to the PACU to continue receiving high care, and they were observed intensively for the first 24 hours. I took a training course about the detail of anesthesia care before starting the investigational research.

In this study I have applied a pharmaceutical care intervention in the three groups equally, as it was previously advised by PC Gordon et al. (2004) who advised that the SA Society of anesthesiologists should be involved with the pharmacist for different improvements (28).

Further comparison study should be done in the future between control group and interventional group of pharmacy care to score the satisfaction deferent between groups.

DOI:10.14753/SE.2013.1821

7. NEW SCIENTIFIC RESULTS AND CONCLUSIONS

New scientific results of the research work were the followings:

- Low dose ketamine hydrochloride can be given safely in spinal fusion, scoliosis, and microdiectomy surgery.

- Low dose ketamine hydrochloride adds advantages to remifentanil intraoperatively, by improving the intraoperative hemodynamic stability (heart rate, mean arterial pressure).

- The intaoperative addition of low dose ketamine hydrochloride exceeds its extraoperative advantages, by affecting the total morphine consumption.

- The addition of low dose ketamine hydrochloride has no influence on total urine output, total blood loss , nor on total time of surgery.

- Low dose ketamine hydrochloride can be added in two stages of the surgery, intra-operatively, and post-operatively in microdisectomy surgery. This can enhance further reduction of the total morphine consumption than when given in one stage.

- The addition of a low dose ketamine hydrochloride both intra- and post-operatively could be an adjunct therapy to maintain postoperative analgesic control whilst reducing postoperative morphine consumption so reducing the nausea and vomiting side effects.

- The addition of low dose ketamine hydrochloride did not show the usual transient psychotic side effect of ketamine in the normal dose.

- I could enhance the use of ketamine hydrochloride in two ways:

  - By focusing on its analgesics mechanism of action in addition to its anesthetic major use.

DOI:10.14753/SE.2013.1821

- By adding low dose to overcome its annoying psychotic side effect in the normal dose.

- Collaborative clinical pharmacy practice on the basis of pharmacology and pharmacodynamic data had an effective role in improving the general outcome of the different surgeries, clinical pharmacist can have many positive roles pre-surgery, during the surgery and in the management of postoperative pain.
- I advise the clinical pharmacist to take a new role in the surgery room.

DOI:10.14753/SE.2013.1821

8. SUMMARY

Intraoperative hemodynamic stability of a patient during surgery, and the requirements for subsequent analgesic consumption due to the severity of the postoperative pain, are all major challenges for the surgical team. Ketamine hydrochloride is an intravenous anesthetic. Its anesthetic and analgesic effects are mediated primarily by a non-competitive antagonism at N-methyl-D-aspartic acid (NMDA) receptors. Low-dose ketamine has a direct analgesic effect, it induces a postoperative morphine-sparing effect and it was proven to decrease post-operative intravenous morphine consumption. In some forms of surgery using a Low-dose infusion of ketamine (1 μg/kg/min) has previously been used intra-operatively and peri-operatively. In this part of the thesis, I intended to implement a new idea to the anesthesiologists to examine the hypothesis that postoperative pain and morphine consumption would be reduced by using the infusion of a very small-dose of ketamine (1 μg/kg/min) both intra- and postoperatively for new types of surgeries were not tested before. This drug was added to an intra-operative remifentanil-based anesthesia regimen for spinal fusion, scoliosis, and lumbar microdiscectomy surgery. Furthermore, I evaluated the effect of ketamine on hemodynamic stability, N-V side effects, and its transient psychotic effects. In the world literature, up to my best knowledge; clinical pharmacists have positive interventional role in the hospital, and in the community pharmacy in controlling chronic diseases, infectious diseases, and on decreasing the expenditure. Hence little information exists about the clinical pharmacist intervention in the surgery room, I conducted a novel idea, by carrying out the clinical pharmacist intervention to the different anesthetics strategies during spinal fusion, scoliosis, and micro discectomy surgery. In this study I have confirmed that adding low dose of ketamine hydrochloride both intra- and post-operatively could be an adjunct therapy to maintain postoperative analgesic control whilst reducing postoperative morphine consumption so reducing the nausea and vomiting side effects in traditional spinal fusion surgery , scoliosis , and lumbar micro discectomy surgery without experiencing ketamine's side effects such as transient psychotic effect. Collaborative clinical pharmacy practice on the basis of pharmacology had an effective role in improving the general outcome of the different surgeries, clinical pharmacist can have many positive roles pre-surgery, during the surgery and in the management of postoperative pain. I advise the clinical pharmacist to take a new role in the surgery room.

DOI:10.14753/SE.2013.1821

9. ÖSSZEFOGLALÁS

A beteg hemodinamikai stabilitásának biztosítása a műtét során, valamint a műtétet követő hatékony fájdalomcsillapítás a sebészeti csapat egyik legnagyobb kihívása.
A ketamin jelentős analgetikus hatással bíró általános anesztetikum, amely hatását az N-metil-D-aszparaginsav (NMDA) receptorok nemkompetitív antagonizmusa révén fejti ki. Alacsony dózisú ketamin közvetlen fájdalomcsillapító hatású, csökkenti a beteg posztoperatív morfin-igényét, így hatékonyan csökkenthető a műtét utáni intravénás morfin adagolás. Korábban már néhány műtéti beavatkozás során alkalmaztak alacsony dózisú (1 μg/kg/min) ketamin infúziót intra- és posztoperatívan. Ennek alapján célul tűztem ki, hogy eddig nem vizsgált sebészeti beavatkozások során tanulmányozzam, hogy kis dózisú (1 μg/kg/perc) ketamin infúzió perioperatív alkalmazása csökkenti-e a műtét utáni fájdalmat, valamint a beteg morfin igényét.
A vizsgálatokban a ketamin adagolása a narkózis intraoperatív kiegészítőjeként történt gerincfúziós műtét, gerincferdülés műtét és ágyéki mikrodiszcektómia során. Értékeltem a ketamin hatását a hemodinamikai stabilitás, a hányinger-hányás és az átmeneti pszichotikus mellékhatások szempontjából is. A szakirodalomban a klinikai gyógyszerész pozitív kórházi és közforgalmú gyógyszertári szerepvállalásáról elsősorban a krónikus betegségek, valamint a fertőző betegségek terápiájának menedzselése során olvashatunk. Kevés információ áll rendelkezésre a klinikai gyógyszerész műtőben végzett gyógyszerészi gondozási tevékenységéről, ezért célul tűztem ki a klinikai gyógyszerészi beavatkozás lehetőségeinek kidolgozását az anesztézia-analgézia stratégiájának kialakításában, gerincfúziós műtét, gerincferdülés műtét és ágyéki mikrodiszcektómia során. Vizsgálataim megerősítették, hogy a hagyományos gerincfúziós műtét, a gerincferdülés és ágyéki mikrodiszcektómia során, adjuváns terápia részeként alkalmazott kis dózisú ketamin, hatékony a posztoperatív fájdalomcsillapító hatás fenntartásában, amely a felhasznált morfin mennyiségének csökkentését, ezáltal a mellékhatásként előforduló hányinger és hányás csökkenését eredményezte, anélkül, hogy ketamin mellékhatásait, mint például az átmeneti pszichotikus hatást, tapasztaltuk volna. A klinikai gyógyszerész, együttműködésben más egészségügyi szakemberekkel, fontos szerepet játszhat a különböző sebészeti eljárások eredményességének javításában, mind a műtéti előkészítés, mind a műtét, mind pedig a posztoperatív fájdalomcsillapítás alatt. A fentiek alapján, javasolom a klinikai gyógyszerész új szerepvállalását a műtéti beavatkozások során.

DOI:10.14753/SE.2013.1821

10. REFERENCES

1. Malcolm-Smith NA, MacMaster MJ. (1983) The use of induced hypotension to control bleeding during posterior fusion for scoliosis. J Bone Joint Surg Br, 65: 255-258.

2. McQuay H, Moore A, Justins D. (1997) Treating acute pain in hospital. Br Med J, 314:1531-1535.

3. Barash PG, Cullen B F, Stoelting R K. Handbook of Clinical Anesthesia (5th Edition) Lippincott Williams & Wilkins, New York, 2006: 167-185.

4. Mao J. (2002) Opioid-induced abnormal pain sensitivity: implication in clinical opioid therapy. Pain, 100: 213-217.

5. Himmelseher S, Durieux M. (2005) Ketamine for perioperative pain management. Anesthesiology, 102: 211-220.

6. Argiriadou H, Papagiannopoulou P, Foroulis CN, Anastasiadis K, Thomaidou E, Papakonstantinou C, Himmelseher S. (2011) Intraoperative infusion of S (+)-ketamine enhances post-thoracotomy pain control compared with perioperative parecoxib when used in conjunction with thoracic paravertebral ropivacaine infusion. J Cardiothor Vasc An, 25(3): 455-461.

7. Hong BH, Lee WY, Kim YH, Yoon SH, Lee WH. (2011) Effects of intraoperative low dose ketamine on remifentanil-induced hyperalgesia in gynecologic surgery with sevoflurane anesthesia. Korean J Anesthesiol, 61(3): 238-243.

8. Zakine J, Samarcq DR, Lorne E, Mubarak, M, Montravers P, Beloucif S, Dupont SH. (2008) Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: A prospective, randomized, double-blind, controlled study. Anesth Analg, 106: 1856–1861.

9. Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Malledant Y. (2003) The effects of small-dose Ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesth Analg, 97: 843-847.

10. Rebel A, Sloan P, Andrykowski M. (2011) Retrospective analysis of high-dose intrathecal morphine for analgesia after pelvic surgery. Pain Res Manag, 16: 19-26.

11. Ribezzi M, Di Venosa N, Nicoletti E, Lauta E, Giuliani R. (2010) The association of tramadol and morphine in the treatment of acute postoperative pain. Minerva Anestesiol, 76: 657-667.

12. Xiao JF, Liu GW, Liu XJ, Hou XM, Gu MN. (2011) Effects of parecoxib on morphine dosage in postoperative patient-controlled analgesia following thoracoscope-assisted thoracotomy. Nan Fang Yi Ke Da Xue Xue Bao, 3: 338-340.

13. Antonio V, Cristina A, Josep MA, Baños JE, Laporte JR. (1999) Management of postoperative pain in abdominal surgery in Spain. A multicentre drug utilization study. Br J Clin Pharmacol, 47: 667-673.

14. Kovac AL.(2000) Prevention and treatment of postoperative nausea and vomiting. Drugs, 59: 213-243.

15. Nortcliffe SA, Shah J, Buggy DJ. (2003) Prevention of postoperative nausea and vomiting after spinal morphine for Caesarean section: comparison of cyclizine, dexamethasone and placebo. Br J Anaesth, 90: 665-670.

16. Bell RF, Dahul JB, Moore RA, Kelso E. (2005) Perioperative ketamine for acute postoperative pain. Acta Anaesthesiol Scand, 49: 1405-1428.

17. FIP, Standards for quality of pharmacy services - Good pharmacy practice. Int Pharm Fed, 1997: 1-7.

18. http://www.fip.org/files/fip/Statements/latest/Dossier%20004%20total.PDF (Last assessed May 10th 2012)

19. Hersberger KE, Arnet I. (2006) Pharmaceutical care - a new discipline in the curriculum: introducing pharmacy students to medication non-compliance. Chimia, 60: 76-79.

20. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. (2006) Clinical pharmacists and inpatient medical care: a systematic review. Arch Intern Med, 166: 955- 964.

21. De Rijdt T, Willems L, Simoens S. (2008) Economic effects of clinical pharmacy interventions: a literature review. Am J Health Syst Pharm, 65: 1161-1172.

22. Reuben SS, Connelly NR. (2000) Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg, 91: 1221-1225.

23. Fountas KN, Kapsalaki EZ, Johnston KW, Smisson HF 3rd, Vogel RL, Robinson JS Jr. (1999) Postoperative lumbar microdiscectomy pain. Minimalization by irrigation and cooling. Spine (Phila Pa 1976), 24: 1958-1960.

24. Damso LB, Frokjaer B, Sondergaard B. Evidence report 3. Follow-up on outcomes of drug therapy (Pharmaceutical Care). Pharmakon, 2003: 1-16.

25. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Estaugh J, Bowie P. (2006) Clinical medication review by a pharmacist of elderly people living in care homes — randomised controlled trial. Age Ageing, 35: 586-591.

26. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM. (2007) Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis, 44: 159-177.

27. Cloete BG, Gomez C, Lyon R, Male BM. (1992) Costs and benefits of multidisciplinary medication review in a long-stay psychiatric ward. Pharm J, 18: 102-103.

28. Gordon PC. (2004) Wrong drug administration errors amongst anaesthetists in a South African teaching hospital. South Afr J Anaesth Analg, 5: 7-8.

29. Craven R. (2007) Ketamine. Anaesthesia, 62: 48-53.

30. Bhutta AT. (2007) Ketamine: a controversial drug for neonates. Semin Perinatol, 31: 303-308.

31. Bjarnesen W, Corssen J. (1967) A new non-barbiturate short acting anesthetic for surgery in burns. Mich Med, 66: 177-181.

32. Tosun Z, Esmaoglu A, Coruh A. (2008) Propofol-ketamine vs propofol-fentanyl combinations for deep sedation and analgesia in pediatric patients undergoing burn dressing changes. Paediatr Anaesth. 18:43-47.

33. Denmark TK, Crane HA, Brown L. (2006) Ketamine to avoid mechanical ventilation in severe pediatric asthma. J Emerg Med, 30: 163-166.

34. Corssen G, Gutierrez J, Reves JG, Huber FC Jr. (1972) Ketamine in the anesthetic management of asthmatic patients. Anesth Analg, 51: 588-596.

35. Stefansson T, Wickström I, Haljamäe H. (1982) Hemodynamic and metabolic effects of ketamine anesthesia in the geriatric patient. Acta Anaesthesiol Scand, 26: 371-377.

36. Tomatir E, Atalay H, Gurses E, Erbay H, Bozkurt P. (2004) Effects of low dose ketamine before induction on propofol anesthesia for pediatric magnetic resonance imaging. Paediatr Anaesth, 14: 845-850.

37. Kohrs R, Durieux ME. (1998) Ketamine: teaching an old drug new tricks. Anesth Analg, 87: 1186-1193.

38. Haas DA, Harper DG. (1992) Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. Anesth Prog, 39: 61–68.

39. Cohen VG, Krauss B. (2006) Recurrent episodes of intractable laryngospasm during dissociative sedation with intramuscular ketamine. Pediatr Emerg Care, 22: 247-249.

40. Canbay O, Celebi N, Sahin A, Celiker V, Ozgen S, Aypar U. (2008) Ketamine gargle for attenuating postoperative sore throat. Br J Anaesth, 100: 490-493.

41. Nayar R, Sahajanand H. (2009) Does anesthetic induction for Cesarean section with a combination of ketamine and thiopentone confer any benefits over thiopentone or ketamine alone? A prospective randomized study. Minerva Anestesiol, 75: 185-190.

42. Leykin Y, Pellis T, Zannier G. (2006) Thiopental-ketamine association and low dose priming with rocuronium for rapid sequence induction of anaesthesia for elective cesareum section. Minerva Anestesiol, 72: 683-688.

43. Hatano S, Sadove MS, Keane DM, Boggs RE, El-Naggar MA. (1976) Diazepam-ketamine anaesthesia for open heart surgery a “micro-mini” drip administration technique. Anaesthesist, 25: 457-463.

44. Filippia A, Nicoletta I, Ismene D, Chryssa P, Theodoros X. (2009) Pharmacological aspects and potential new clinical applications of ketamine: Reevaluation of an old drug. J. Clin. Pharmacol, 49: 957- 964.

45. Suppa E, Valente A, Catarci S, Zanfini B, Draisci G. (2012) A study of low-dose S-ketamine infusion as "preventive" pain treatment for cesarean section with spinal anesthesia: benefits and side effects. Minerva Anestesiol, 78: 774-781.

46. Parikh B, Maliwad J, Shah VR. (2011) Preventive analgesia: Effect of small dose of ketamine on morphine requirement after renal surgery. J. Anaesthesiol Clin Pharmacol, 27: 485-488.

47. Lavand'homme P, De Kock M, Waterloos H. (2005) Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology, 103: 813-820.

48. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF. (2000) Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesth Analg, 90: 1419-1422.

49. Guignard B, Coste C, Costes H, Sessler DI, Lebrault C, Morris W, Simonnet G, Chauvin M (2002) Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesth Analg, 95: 103-108.

50. Suzuki M, Tsueda K, Lansing PS, Tolan MM, Fuhrman TM, Ignacio CI, Sheppard RA. (1999) Small-dose ketamine enhances morphine-induced analgesia after outpatient surgery. Anesth Analg, 89: 98-103.

51. Becke K, Albrecht S, Schmitz B, Rech D, Koppert W, Schüttler J, Hering W. (2005) Intraoperative low-dose S-ketamine has no preventive effects on postoperative pain and morphine consumption after major urological surgery in children. Paediatr Anaesth, 15: 484-490.

52. Kissin I, Bright CA, Bradley EL Jr. (2000) The effect of ketamine on opioid-induced acute tolerance: Can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? Anesth Analg, 91: 1483-1488.

53. Urban MK, Jules-Elysee K, Urquhart B, Cammisa FP, Boachie-Adjei O. (2002) Reduction in postoperative pain after spinal fusion with instrumentation using intrathecal morphine. Spine (Phila Pa 1976), 27: 535-537.

54. Jirarattanaphochai K, Sae-Jung S. (2008) Nonsteroidal antiinflammatory drugs for postoperative pain management after lumbar spine surgery: a meta-analysis of randomized controlled trials. J Neurosurg Spine, 9: 22-31.

55. Schenk MR, Putzier M, Kügler B, Tohtz S, Voigt K, Schink T, Kox WJ., Spies C, Volk T. (2006) Postoperative analgesia after major spine surgery: patient-controlled epidural analgesia versus patient-controlled intravenous analgesia. Anesth Analg, 103: 1311-1317.

56. Borgeat A, Blumenthal S. (2008) Postoperative pain management following scoliosis surgery. Curr Opin Anaesthesiol, 21:313-316.

57. Bourke DL, Spatz E, Motara R, Ordia JI, Reed J, Hlavacek JM. (1992) Epidural opioids during laminectomy surgery for postoperative pain. Epidural opioids. J Clin Anesth, 4: 277-281.

58. Thienthong S, Jirarattanaphochai K, Krisanaprakornkit W, Simajareuk S, Tantanatewin W, Sathitkarnmanee A. (2004) Treatment of Pain after Spinal Surgery in the Recovery Room by Single Dose Lornoxicam: A Randomized, Double Blind, Placebo-Controlled Trial. J Med Assoc Thai, 87: 650-655.

59. Entwistle MA, Patel D. (2006) Scoliosis surgery in children. Continuing Education in Anaesthesia. Critical Care & Pain, 6: 13-16.

60. Mikael RL, Brown TR, Lazarus HL, Vinson MC. (1975) Quality of pharmaceutical care in hospitals. Am J Hosp Pharm, 32: 567-574.

61. Hepler CD, Grainger-Rousseau TJ. (1995) Pharmaceutical care versus traditional drug treatment. Is there a difference? Drugs, 49: 1- 10.

62. Hepler CD. (1990) The future of pharmacy: pharmaceutical care. Am Pharm, NS30(10): 23-29.

63. Hepler CD, Strand LM. (1990) Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm, 47: 533-543.

64. Cipolle RJ, Strand LM, Morley PC. Pharmaceutical Care Practice, McGraw Hill Higher Education, New York, 1998.

65. Bond, C. (2009) An evidence base for professional competence. Int J Pharm Pract, 17: 77.

66. ESCP. (European Society of Clinical Pharmacy). What is clinical pharmacy? http://www.escpweb.org (Last assessed 26th February 2010).

67. Hill P, Dowse R. (2007) Cognitive pharmaceutical services and the community pharmacist: are South African patients receiving them and are they willing to pay? Int J Pharm Pract,15: 201-208.

68. Farris KB, Fernandez-Llimos F, Benrimoj SI. (2005) Pharmaceutical care in community pharmacies: practice and research from around the world. Ann Pharmacother, 39: 1539-1541.

69. Frokjaer B, Sondergaard B, Herborg H. Evidence report 3. Follow-up on outcomes of drug therapy (Pharmaceutical Care). Pharmakon, 2003: 1-16.

70. Blenkinsopp A, Hassey A. (2005) Effectiveness and acceptability of community pharmacy-based interventions in type 2 diabetes: a critical review of intervention design, pharmacist and patient perspectives. Int J Pharm Pract, 13: 231-240.

71. Roughead EE, Semple SJ, Vitry AI. (2005) Pharmaceutical care services: A systematic review of published studies, 1990 to 2003, examining effectiveness in improving patient outcomes. Int J Pharm Pract, 13: 53-70.

72. Bond CA, Raehl CL. (2007) Clinical and economic outcomes of pharmacist-managed antimicrobial prophylaxis in surgical patients. Am J Health Syst Pharm, 64: 1935-1942.

73. Wubben DP, Vivian EM. (2008) Effects of pharmacist outpatient interventions on adults with diabetes mellitus: a systematic review. Pharmacotherapy, 28: 421-436.

74. Machado M, Bajcar J, Guzzo GC, Einarson TR. (2007) Sensitivity of patient outcomes to pharmacist interventions. Part II: Systematic review and meta-analysis in hypertension management. Ann Pharmacother, 41: 1770-1781.

75. Machado M, Nassor N, Bajcar J, Guzzo GC, Einarson TR. (2008) Sensitivity of patient outcomes to pharmacist interventions. Part III: systematic review and meta-analysis in hyperlipidemia management. Ann Pharmacother, 42: 1195- 1207.

76. Hanlon JT, Lindblad CI, Gray SL. (2004) Can clinical pharmacy services have a positive impact on drug-related problems and health outcomes in community-based older adults? Am J Geriatr Pharmacother, 2: 3-13.

77. Holland R., Desborough J, Goodyer L, Hall S, Wright D, Loke YK. (2008) Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol, 65: 303-316.

78. Tonna AP, Stewart D, West B, Gould I, McCaig D. (2008) Antimicrobial optimization in secondary care: the pharmacist as part of a multidisciplinary antimicrobial programme—a literature review. Int J Antimicrob Agents, 31: 511-517.

79. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. (1990) Drug-related problems: their structure and function. DICP, 24: 1093-1097.

80. Segal R. Therapeutic outcomes monitoring: a method for implementing pharmaceutical care, in Health outcomes and pharmaceutical care: measurement, applications and initiatives. Pharmaceutical Products Press, an imprint of the Haworth Press, Inc., Binghamton, 1996: 193-198.

81. Eichenberger PM, Pharmaceutical Care Practice - Drug-related Problems and Opportunities for New Services. Ph.D. Thesis, Basel, 2010: 28.

82. Westbrook JI, Rob MI, Woods A, Parry D. (2011) Errors in the administration of intravenous medications in hospital and the role of correct procedures and nurse experience. BMJ Qual Saf, 20: 1027-1034.

83. Paulino EI, Bouvy ML, Gastelurrutia MA, Guerreiro M, Buurma H (2004) Drug related problems identified by European community pharmacists in patients discharged from hospital. Pharm World Sci, 26: 353-360.

84. Winterstein AG, Sauer BC, Hepler CD, Poole C. (2002) Preventable drug-related hospital admissions. Ann Pharmacother, 36: 1238-1248.

85. Beijer HJ, de Blaey CJ. (2002) Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci, 24: 46-54.

86. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. (1997) Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA, 277: 301-306.

87. Lau HS, Florax C, Porsius AJ, De Boer A. (2000) The completeness of medication histories in hospital medical records of patients admitted to general internal medicine wards. Br J Clin Pharmacol, 49: 597-603.

88. Guidelines for Residential Medication Management Review and Quality Use of Medicines services (http://www.psa.org.au/download/practice-guidelines/rmmr-and-qum-services.pdf ; Last assessed 11th May 2012)

89. Brookes K, Scott MG, McConnell B. (2000) The benefits of hospital based community services liaison pharmacist. Pharm World Sci, 22: 33-38.

90. Bootman JL, Harrison DL, Cox E. (1997) The health care cost of drug-related morbidity and mortality in nursing facilities. Arch Intern Med, 157: 2089-2096.

91. Schmidt I, Claesson CB, Westerholm B, Nilsson LG, Svarstad BL. (1998) The impact of regular multidisciplinary team interventions on psychotropic prescribing in Swedish nursing homes. J Am Geriatr Soc, 46: 77-82.

92. Lipton HL, Bero LA, Bird JA, McPhee SJ. (1992) The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. Med Care, 30: 646-658.

93. Bjornson DC, Hiner WO, Jr., Potyk RP, Nelson BA, Lombardo FA, Morton TA, Larson LV, Martin BP, Sikora RG, Cammarata FA. (1993) Effect of pharmacists on health care outcomes in hospitalized patients. Am J Hosp Pharm, 50: 1875-1884.

94. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, Bates DW. (1999) Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA, 282: 267-270.

95. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. (1995) A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med, 333: 1190-1195.

96. Palaian S, Prabhu M, Shankar PR. (2006) Patient counseling by pharmacist - A focus on chronic illness. Pak J Pharm Sci, 19: 62-65.

97. Shoemaker SJ, de Oliveira DR, Alves M, Ekstrand M. (2011) The medication experience: Preliminary evidence of its value for patient education and counseling on chronic medications. Patient Educ Couns, 83: 443-450.

98. Taitel M, Jiang J, Rudkin K, Ewing S, Duncan I. (2012) The impact of pharmacist face-to face counseling to improve medication adherence among patients initiating statin therapy. Patient Prefer Adherence, 6: 323- 3239.

99. Kuwajerwala NK, Reddy RC, Kanthimathinathan VS, Siddiqui RA. Perioperative Medication Management. http://emedicine.medscape.com/article/284801-overview (Last assessed 24th September 2012).

100. Barone CP, Lightfoot ML, Barone GW. (2003) The postanesthesia care of an adult renal transplant recipient. J Perianesth Nurs, 18: 32- 41.

101. http://www.surgeryencyclopedia.com/Pa-St/Postoperative-Care.html#b (Last assessed 11th June 2012).

102. http://www.merckmanuals.com/professional/special_subjects/care_of_the_surgical_patient/postoperative_care.html (Lat assessed 11th June 2012).

103. Samra SK, Dy EA, Welch KB, Lovely LK, Graziano GP. (2001) Remifentanil and fentanyl-based anesthesia for intraoperative monitoring of somatosensory evoked potentials. Anesth Analg, 92: 1510-1515.

104. Morgan GE, Mikhail M, Murray M. Clinical anesthesiology, 4th Edition. Mc Graw-Hill Medical, USA, 2006: 359–410.

105. Wong GTC, Yuen VMY, Chow BFM, Irwin MG. (2007) Persistent pain in patients following scoliosis surgery. Eur Spine J, 10: 1551-1556.

106. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. (1997) Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand, 41: 1124-1132.

107. Javery KB, Ussery TW, Steger HG, Colclough GW. (1996) Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth, 43, 212-215.

108. Mastronardi L, Pappagallo M, Puzzilli F, Tatta C. (2002) Efficacy of the morphine-Adcon-L compound in the management of postoperative pain after lumbar microdiscectomy. Neurosurgery, 50: 518-524.

109. Hadi BA, Al Ramadani R, Daas R, Naylor I, Zelko R, Saleh M. (2009) The influence of anaesthetic drug selection for scoliosis surgery on the management of intraoperative haemodynamic stability and postoperative pain – pharmaceutical care programme. SAJAA, 15: 10-14.

110. Hadi BA, Al Ramadani R, Daas R, Naylor I, Zelkó R. (2010) Remifentanil in combination with ketamine versus remifentanil in spinal fusion surgery-a double blind study. Int J Clin Pharmacol Ther, 48: 542-548.

111. Kundra P, Gurnani A, Bhattacharya A. (1997) Preemptive epidural morphine for postoperative pain relief after lumbar laminectomy. Anesth Analg, 85: 135-138.

112. Chia YY, Liu K, Liu YC, Chang HC, Wong CS. (1998) Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic concentration. Anesth Analg, 86: 1245-1249.

113. Snijdelaar DG, Cornelisse HB, Schmid RL, Katz J. (2004) A randomised, controlled study of peri-operative low dose S (+)-ketamine in combination with postoperative patient-controlled S (+)-ketamine and morphine after radical prostatectomy. Anaesthesia, 59: 222-228.

114. Webb AR, Skinner BS, Leong S, Kolawole H, Crofts T, Taverner M, Burn SJ. (2007) The addition of a small-dose ketamine infusion totramadol for postoperative analgesia: a double-blinded, placebo-controlled, randomized trial after abdominal surgery. Anesth Analg, 104: 912-917.

115. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. (2005) Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee artheroplasty. Anesth Analg, 100: 475-480.

116. Gu X, Wu, X, Liu, Y, Cui S, Ma Z. (2009) Tyrosine phosphorylation of the N-Methyl-D-Aspartate receptor 2B subunit in spinal cord contributes to remifentanil-induced postoperative hyperalgesia: the preventive effect of ketamine. Mol Pain, 5: 76. doi:10.1186/1744-8069-5-76

DOI:10.14753/SE.2013.1821

11. OWN PUBLICATIONS RELATED TO THE THESIS

1. **Hadi BA**, Al Ramadani R, Daas R, Naylor I, Zelko R, Saleh M. (2009) The influence of anaesthetic drug selection for scoliosis surgery on the management of intraoperative haemodynamic stability and postoperative pain – pharmaceutical care programme. SAJAA, 15: 10-14.

2. **Hadi BA**, Al Ramadani R, Daas R, Naylor I, Zelkó R. (2010) Remifentanil in combination with ketamine versus remifentanil in spinal fusion surgery-a double blind study. Int J Clin Pharmacol Ther, 48: 542-548.

3. **Hadi BA**, Daas R, Zelko R. A randomized, controlled trial of a clinical pharmacist intervention in microdiscectomy surgery- low dose intravenous ketamine an adjunct to standard therapy. Elsevier, Saudi Pharm J, doi: 10.1016/j.jsps.2012.08.002

DOI:10.14753/SE.2013.1821

12. ACKNOWLEDGEMENTS

I am owing to render thanks first of all for my tutor Prof. Romána Zelkó for her continuous and irreplaceable support and for providing several idea and advice during my work.

I thank my family; namely my "Father" Mr. A. Lattif. A. Hadi for the encouragement to take the first step for the PhD.

I wish to express my gratitude to my sons "Sami & Tariq" and my husband "Dr R. Rasheed" for their patience.

Many thanks belong to Dr R. Daas and Dr M. Saleh for the clinical support.

I give thanks to the head of Arab Center Hospital/Jordan, the Specialty Hospital/Jo, and Péterfy Sándor utcai Kórház / Hu, for giving me the chance to do the practical part in the hospitals.

I give thanks to Prof. Marwan Kamal president of Philadelphia University/ Jo, Prof. M.Ameen Awwad, and Prof. S. Abu Osbaa Vice presidents of the University, Prof. A. Jaber the present Dean of Faculty of Pharmacy, and to (Prof. Adi Areda the X dean of the Faculty) for facilitating my load, and the different support they provide me with during the research period at my work place.

I deeply thank Dr I. Naylor for the distance support from UK in different ways, and many ways.

I thank Mr. N. Atabeh, Mr. M. Araishi, Ms. A. Hadadien, Dr S. Sbaitan, Dr S. Tolfah, and Dr M. Shawakfeh for technical support.

Many thanks go to all my friends in Jordan, and in Hungary, who supported me and for being around me all the time.

DOI:10.14753/SE.2013.1821

13. OFFPRINTS OF THE PUBLICATIONS