

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

Ph.D. thesis

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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 fejt ki. Alacsony dózisu 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 dózisu (1 µg/kg/min) ketamin infúziót intra- és posztoperatíván.

Ennek alapján célul tűztem ki, hogy eddig nem vizsgált sebészeti beavatkozások során tanulmányozzam, hogy kis dózisu (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 gyógyszerértési 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 dózisu ketamin, hatékony a posztoperatív fájdalomcsillapító hatás fenntartásában, amely a felhasznált morfin mennyiségének csökkentését, ezáltal a mellékhatásként előforduló hányinger és hányás csökkenését eredményezte, anélkül, hogy a 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 poszt-operatív fájdalomcsillapítás alatt.

A fentiek alapján, javaslom a klinikai gyógyszerész új szerepvállalását a műtéti beavatkozások során.

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 intervene 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 remifentanyl-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.

INTRODUCTION

Intra-operative 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. Remifentanyl 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. 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 remifentanyl in that the post-operative residual effect is minimal.

In contrast to the pharmacological effects of remifentanyl, 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.

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 and also induces a postoperative morphine-sparing effect in some forms of surgery. Using a Low-dose infusion of ketamine (1 $\mu\text{g}/\text{kg}/\text{min}$) has previously been used intra-operatively in different types of surgery and used peri-operatively in major abdominal surgery, and also to decrease post-operative intravenous morphine consumption. Many surveys have shown a high prevalence of significant pain after many types of surgery and regulation of such postoperative pain is one of the most common therapeutic problems in hospitals.

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, nausea and vomiting are the most common therapeutic problems in hospitals and many surveys have shown high prevalence of significant pain and N-V after all types of major surgery. Reducing the opioids dose can lead to a lower incidence of N-V.

Clinical pharmacists offer pharmaceutical care to improve patients' health, in addition to dispensing medications; 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.
2. Patient education and counselling (illness, medication, healthy lifestyle, treatment goals, need for compliance with medication regimens and facilitating communication with physicians).
3. Monitoring patient symptoms and outcomes.

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.

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.

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 hemodynamic 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.

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. In addition to that, clinical pharmacist had positive impact on decreasing the expenditure.

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.

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.

OBJECTIVES

1. My aim was to intervent 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.

2. 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,
3. 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.
4. To monitor the influence of lowering morphine consumption on the nausea and vomiting side effect.
5. To monitor if ketamin low dose induces any regular side effects; which usually occur in the normal dose as hallucination.
6. To involve the pharmacist special pharmacodynamic and pharmacolglcal 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.
7. 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.

METHODS

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 microdiescectomy surgery under pharmaceutical care program.

Patient selection (inclusion and exclusion criteria for patients undergoing the three types of surgeries)

A total number of 115 patients were involved in a randomized control trial , divided into 30, 40, 45 in spinal fusion, scoliosis, and microdiscectomy surgeries respectively.

Male and females were involved in the study in the following way; in spinal fusion surgery G1 (3 male-12 female) ,and G2 (7- 8). In scoliosis surgery G1 (8 male – 12 female) and G2 (7 male- 13 female) were involved, while in microdiscectomy G1 (8 male -7 female), G2 (7 male -8 female), and G3 (6 male -9 female). All patients were adults, their range of ages were 49-59 years for spinal fusion, 19-24 years for scoliosis, and 49-58 years for microdiscectomy surgery. Patient included had lumber and thoracic spinal fusion surgery, more than 40°curvature for scoliosis surgery, and a lumber microdiscectomy, all patients were of acceptable educational level to cope with the pharmaceutical intervention, and none were addicted to narcotic therapy in order to have accurate results.

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 recemic ketamine (Tekam Al-Hikma, Jordan) infusion at a dose of

1µg/kg/minutes in G2 administered in 2 different cannulas in spinal fusion and scoliosis surgeries.

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.

All drugs were stopped at the end of the operation, 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, except for G3 in microdiscectomy surgery where the ketamine was continued to be administered at 1 µg/kg/min for 24h.

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 groups. Group 3 in spinal fusion surgery received an additional infusion of ketamine 1µg/kg/min for 24 hours, whereas the other simply received the placebo – 0.9% normal saline.

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.

In spinal fusion and scoliosis surgeries 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.

While in microdiscectomy surgery 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.

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.

In spinal fusion and scoliosis surgeries data were expressed as mean \pm 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 calculation 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 \pm 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 be statistically significant.

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

Introducing the 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 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. 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.

NEW SCIENTIFIC RESULTS

- Low dose ketamine hydrochloride can be given safely in spinal fusion, scoliosis, and microdisectomy surgery.
- Low dose ketamine hydrochloride adds advantages to remifentanyl intraoperatively, by improving the intraoperative hemodynamic stability (heart rate, mean arterial pressure).
- The intraoperative 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, intraoperatively, 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 analgesic mechanism of action in addition to its anesthetic major use.
 - 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.

LIST OF PUBLICATION

Publications

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, 48:542-8.
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. Saudi Pharm J. doi: 10.1016/j.jsps.2012.08.002

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1. **Hadi, BA**. The clinical pharmacist role in anesthesia – a double blind study. *The Third Kuwait International Pharmacy Conference (KIPIC 2011)* 14-16 February, **2011**, Radisson Blue /Kuwait.
2. **Hadi, BA**. Remifentanil in combination with ketamine versus remifentanil in spinal fusion surgery – a double blind study. *The 13th Jordan Pharmacist Conference* 22-24 April **2010**, Amman-Jordan.
3. **Hadi, BA**, Abbas, T, Zelkó, R., Ian, N. A drug utilization study during scoliosis surgery – an analysis of the past to optimize drug use in the future. *2nd PharmSciFair*, 8-12 June **2009**, Nice, France. Book of abstract, p. 118., P-78.

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