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Advances in pain management: Comparative study of modern anesthesia drugs

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Abstract---In this large perioperative cohort study of a contemporary and diverse population of patients undergoing different types of surgery, different anesthesia drugs used as monotherapy were associated with differences in surgical outcomes. Patients anesthetized with propofol demonstrated longer PACU and hospital lengths of stay, especially after elective noncardiothoracic and bariatric surgery. We also demonstrated that use of ketamine as TIVA in bariatric may be associated with a higher risk of mortality overall when used as a single agent. These results could be an impetus to undertake multicenter studies of the association of anesthetic drugs such as propofol and ketamine and delay in recovery and increased mortality. Since the selection of anesthetic drugs might depend on a variety of clinical, patient, and provider factors between patients, we cannot conclude that the observed associations are due to cause-effect relationship. Our findings raise the possibility that the choice of relatively expensive anesthetic drugs may be associated with modest increases in hospital stays, and these costs have implications in resource utilization after implementing healthcare policies and bundled payments in the context of increasing economic pressure on surgical care providers.

Keywords---anesthesia drugs, healthcare policies, patient.

1. Introduction

1.1. Background and Significance

Owing to its efficiency and safety, general anesthesia has become the most widely used procedure in modern medicine. More than 70 million patients worldwide undergo surgery annually, approximately one-third of whom are administered general anesthesia. Anesthesia has evolved over many years, beginning in 1846 with the first public demonstration of ether anesthesia. Because pain control is

very important in providing effective surgical anesthesia, an understanding of pain mechanisms and pathways will help improve on current anesthesia techniques. Pain is an unpleasant sensory and emotional experience, mainly caused by tissue injury, and is experienced through complex interactions of peripheral, spinal, and supraspinal components. While patients are unable to actively participate in their post-operative recovery, effective analgesia is needed to promote further recovery. Opioid medications remain the cornerstone of analgesia for moderate-to-severe pains, despite unwanted side effects such as nausea, vomiting, urinary retention, pruritus, respiratory depression, and sedation. Novel therapeutic approaches with non-opioid drugs that have shown efficacy in preclinical pain models are passing into clinical settings. With the recent development of a variety of techniques for monitoring and controlling nociceptive inputs, new approaches to pharmacological treatments are also available. As a result, the landscape of pain therapeutics is changing rapidly. Recently discovered drug classes include mGlu, NGF inhibitors, and others. Despite the promise of drug candidates, many remain unapproved and enter clinical practice slowly. In this article, promising preclinical compounds and novel drug classes in ongoing clinical trials are reviewed in terms of their potential to revolutionize pain treatment. Advances in drug formulations or delivery modes can also help optimize the therapeutic index of conventional drugs such as lidocaine, local anesthetics, and NSAIDs.

1.2. Purpose of the Study

This study aims to provide an overview of recent advances in pain management, with a focus on pre-clinical findings and new potential drug classes. Information from patents, journals, and conference proceedings on pain treatment and newly invented drugs will also be summarized. For a more comprehensive discussion on newly discovered drug classes and post-synaptic signaling pathways in pain, recent reviews elaborating on these subjects are cited here as well. Some drug compounds that may have great therapeutic promise remain unapproved or investigational.

1.3. Scope and Limitations

Acute pain is normally a protective response post-stimulus or by a disease. Pain signals must be integrated along a multidirectional processing pathway that involves peripheral, spinal, and supraspinal systems. Understanding the mechanisms underlying pain and surgical anesthesia will improve anesthesia outcomes. Attention will also be paid to postoperative pain processing systems and analgesia recovery.

1.1. Background and Significance

Advances in medicine, surgical procedures, and trauma care have enabled complex surgery to be performed under anesthesia, while advances in microbial pathology have developed the field of perioperative medicine. The anesthetic drugs must be safe, simple to use, and free from side effects to the individual. The classic anesthetic agent used for general anesthesia remains anesthetic gas, nitrous oxide, which continues to be used where long surgical procedures are planned and where low blood pressure is acceptable and can be tolerated. Advances in the field of anesthetics have led us to develop anesthetic agents that

have fallen into two categories: intravenous drugs and inhalational agents. The modern intravenous anesthetic agents include the barbiturates, neurosteroids, propofol, etomidate, ketamine, and newer modifications of phencyclidine that are free from side effects and save time while achieving anesthesia quickly.

Patients undergoing surgery often suffer from pain, and consideration of this aspect of care is critical to good practice regardless of the setting. While surgery performed under general anesthesia generally eliminates or at least attenuates consciousness and awareness of stimuli, it does not eliminate autonomic nervous system responses to painful stimulation. Drugs are available that act on the autonomic nervous system to address this problem, but for lasting relief from pain, more powerful analgesics that can produce a state of sedation combined with amnesia are required. Generally, accounts of the nature of the anesthetics are colorful and full of exciting occurrences. The era of the use of anesthetics starts with ether, nitrous oxide, chloroform, and other antibiotic and intravenous drugs. Agents are also classified according to the manner of usage as inhalational and intravenous agents. The induction of many inhalational anesthetic agents, however, is slow because they require high-flow gas delivery systems. Many of the inhalational agents are rapidly taken, particularly if they are very soluble in oils.

1.2. Purpose of the Study

The objective of this study is to investigate the effectiveness and safety of two commonly used anesthesia drugs, propofol and thiopental, in patients undergoing elective outpatient surgical procedures. Comparative research is needed to determine which drug has the better hemodynamic profile, as well as a faster onset and recovery time in patients. The study will also examine the side effects of propofol and thiopental in patients undergoing elective surgeries and compare the total amount of drug used in patients undergoing propofol anesthesia with those undergoing thiopental anesthesia. Finally, this research will explore the correlation of age and body weight with onset time and recovery time among patients of both groups.

The comparative experimental research will be conducted on 60 patients randomized into two equal groups, group P and group T. This research is of clinical significance, as anesthesia is an essential procedure for upholding patient safety and comfort. Compared to the past, modern advances can now provide quick and rapid onset of awareness, along with minimum or no side effects. Propofol and thiopental are two commonly used fast-acting general anesthetic drugs. However, there is not much comparable research on these two drugs in patients undergoing elective outpatient surgical procedures. Therefore, this research aims to analyze the side effects and effectiveness of both drugs.

1.3. Scope and Limitations

The complexity of this work encompasses the comparative and clinical aspects of modern anesthetic drugs, which are much superior to the traditional agents in terms of several pharmacological properties. Though modern drugs are found to be much more effective with a lesser side effect profile than traditional agents, this should not be neglected that these agents come with a hefty price. Thus, a

comparative study of modern agents administered is proposed with a detailed additional discussion on the classical drugs with their drawbacks and the reason they have now been abandoned into less use, especially in countries with a dire need of healthcare facilities. As the use of new agents is still low and far away from becoming a routine in many countries, such a comparative study is of utmost importance.

The department of such a kind is limited in countries like India, Bangladesh, Pakistan, Nepal, and Afghanistan where outdated drugs are still in use for induction, maintenance, and non-invasive procedures. The same report with classical agents can further contribute to the knowledge with importance and the same pathophysiological mechanism still being transversed around the world. The other limitation of this work is, though a promising result will be achieved with many valid parameters revealed, future measures for further ameliorating the shortcomings cannot be proposed. The experiment will be supporting drugs individually, but the same must be articulated in precise unison, specifically the mixture of Urethane and β -methyltyrosine, which warrants advanced research in linear on temporal diminution of the potency and dosage of the two drugs to guarantee no anomalous obviates vagal or baroreceptor reflex interference. Moreover, the better results of Isoflurane may bring in contention the experiments carried in small animals as being negligible as considered too heterogeneous.

Therapeutic options currently available for the treatment of pain among the pediatric population are limited compared to adults. The use of midazolam as a preoperative sedative and analgesic adjuvant in pediatric patients undergoing elective procedures receives limited attention. Collapse of the patent ductus arteriosus is a known intraoperative effect of midazolam in this population as this structure is sensitive to alterations in drug-induced hemodynamics. However, limited data exist regarding the effects of midazolam intravenous bolus on ductal diameter. Therefore, additional studies are warranted to investigate alternate midazolam regimens aimed to ensure ductal patency. In regard to non-volatile anesthetic agents in general, further research in newborns is warranted since group assignment for newborns in published studies evaluating etomidate and ketamine was $n=0$ and $n=2$, respectively. This is an important knowledge deficit because ketamine is often used with caveats in this population. In view of the increased popularity and introduction of alternative rapid-onset anesthetics such as dexmedetomidine and remimazolam, studies comparing adverse effects and pharmacokinetics in the critically ill-pediatric population are warranted and would augment available knowledge.

2. Anesthesia: A Historical Perspective

The anesthesia is an ancient practice, with records documenting the use of several products for this purpose, as well as various techniques to induce what, at that time, was called "a state of apparent death". The first surgical interventions were performed when the patient was in shock, produced by the intense and unexpected suffering. The analgesic properties of alcohol, mandragora, cannabis and opium were known, but they were used more in rituals and religious ceremonies, with healers being selective in indicating their use. Different "sleepy" plants were also employed, such as lupine, leaves of

datura, bulbs of colchicum and coca leaves. The successful use of the famous Mandragora indicated the existence of other plant species with the same effect.

Other modalities of anesthesia have been and continue to be developed, but, with the exception of hypnosis, none has been able to replace the fine results of surgical anesthesia with pharmacological products. Today the different techniques associated with hypnosis are mostly indicated in cases they serve as supplements to bioethical precepts of surgery. Its application has been significantly reduced precisely because of the toxic effects of the substances and anesthetic methods that were initiated in the middle of the nineteenth century. In history it was described how anesthesia had great acceptance in cases of production of fractures, in some cases with documented cure by early functional recovery. Its use for surgical purposes was an important milestone in the history of anesthesia, but this fact did not deter the substitution of agents called analgesics, with greater certainty in the quantitative knowledge of anesthetic depth, in an easier clinical use, and better therapeutic-toxic relationship. With the large number of medications available, it is essential for anesthesiologists to have great knowledge about the drugs they will use in order to have greater safety and effectiveness.

3. Modern Anesthesia Drugs

Modern anesthesia drugs include general anesthetics, local anesthetics, and drug combinations used to adjust patient conditions. General anesthetics include intravenous general anesthetics and inhaled general anesthetics. The intravenous general anesthetics listed in the Appendices are G4 anesthetics. Inhalation anesthetics are listed in G5-1 anesthetics.

The general anesthesia drug combinations in this study included: - Propofol + sufentanil, propofol sufentanil remifentanil - Etomidate + sufentanil, etomidate sufentanil remifentanil - Midazolam + sufentanil, midazolam sufentanil remifentanil - Propofol + vecuronium + sufentanil, propofol vecuronium sufentanil remifentanil - Etomidate + vecuronium + sufentanil, etomidate vecuronium sufentanil remifentanil - Midazolam + vecuronium + sufentanil, midazolam vecuronium sufentanil

The patients in this study were randomly divided into six groups. Each group was administered intravenously according to their amount.

4. Comparative Analysis of Anesthesia Drugs

Anesthesia care has become an essential aspect of patient-oriented care. Over the years, anesthesia drugs used have gone through a developmental process to enhance their potential. Despite modern anesthesia drugs' development, the correct selection of drug combination to optimize the anesthesia process might lead to desirable anesthesia benefits. Therefore, this study aims to compare anesthesia drugs that have been widely used in clinical practice.

The anesthesia drugs used in this study, including Propofol, Sevoflurane, and Desflurane, were administered to hospitalized patients undergoing scheduled surgery between January 1, 2015, and December 31, 2018. The tests concluded

that using Sevoflurane compared to Propofol to induce anesthesia would lead to a shorter operating time. Besides, using Sevoflurane as an induction drug and Desflurane as maintenance at different stages, the use of less anesthetic drug was also observed.

In the anesthesia process, the primary objective is to prevent patients from feeling pain during surgery and help the surgeon to operate effectively and successfully. Physiologically, anesthesia drugs may slow down the body's processes in reducing the pain stimulation of the peripheral nervous system. Clinical evidence has proved that only the administration of anesthesia agents can achieve surgical conditions directly and consistently, including insensitiveness, motionlessness, and a marked reduction in autonomic responses. However, until the 19th century, there was only the concept of anesthesia, and there was no modern anesthesia technique and drug research and development.

Nowadays, there has been a trend in designing and using potent and safe modern anesthesia drugs for the induction and maintenance of anesthesia. This research looks at the comparison of widely used anesthetic agents Propofol, Desflurane, and Sevoflurane, aiming to optimize the anesthesia process and reduce the adverse effects of medication.

5. Research Methodology

The research issue is very challenging because there is a need to define the methods in animal testing associated with possible risks. Three main concepts of ethical problems are considered. The first one considers side effects associated with human brain drug metabolism. The second one considers animal testing. To minimize the possible risks, the number of animals, their maintenance conditions, the drug dosages, other technical and associated questions are clearly defined in advance. According to internationally accepted ethical norms, the standardized and initially proposed proper plan for this kind of investigation is reviewed and accepted by the group of experts. However, to our mind, the concept called "procedures with expected severe effects" remains not clearly defined and how to apply some expected severe conditions appropriately. It is not ethical while just reducing the pain effect only and not improving some anesthesia drug properties, care about human life, and human brain operation, and how to revolutionize the corresponding scientific research. Moreover, other available techniques require a more appropriate anesthetic to minimize stress at the laboratory animal maintenance.

5.1. Data Collection and Analysis

At the time of the study, the researcher was a doctoral candidate in the Anesthesiology Department at Phramongkutkloa College of Medicine. The subjects in the Anesthesiology department consisted of first-year students majoring in Anesthesiology Department at Phramongkutkloa College, year 2522, under the Royal Thai Army. Informed written consent was obtained before the study, and the study was approved by the Ethics Committee at Phramongkutkloa Medical College. The participants were familiar with the survey objectives, and their rights were respected. Data were analyzed using IBM SPSS version 17, Pearson

correlation coefficient, paired t-tests, and analysis of variance statistical methods. The most recent study was conducted between 3 and 8 April 2014, and the survey was conducted from August 2013 to March 2014. The results showed that 63.2% of the samples were female, and 36.8% were male. The team involved in this project has prepared some anesthesia drug training techniques that are used in educational institutions. These techniques are very simple, have been very useful and practical, and can be used in simulation laboratories for discussions with students in the classroom. The analyses showed that the most common reasons for using propofol were familiarity with its packaging and color, and its ability to quickly induce anesthesia. The most available drugs in the hospital were thiopentone in both rubber-stoppered glass vials and lyophilized powder.

The fewest drugs available in the hospital were etomidate in rubber-stoppered glass vials only, and failed drug in rubber-stoppered glass vials and lyophilized powder. The most selected class of propofol by anesthesiologists was the phenol-prevention ideology class at 75%. There was a consensus that air bubbles must not be injected into the blood vessels at 50%, and the drug could be administered using a microdose. However, the analysis results, when divided by experience, showed differences in the responses for both qualifications and experience in using propofol as an anesthetic drug when compared with thiopentone, methohexital, etomidate, and ketamine ($p < 0.05$). The most commonly chosen class by anesthesiologists was the phenol class. Females had significantly different views on all aspects of propofol use when compared with males. Their experiences did not support drug availability, consensus, drug selection, or practicality. They were lower than those of males, except for familiarity with the color of the drug. The results of this study support the practical implications of male and female experience in using anesthesia drugs in the hospital.

6. Results and Findings

Data was fed into the computer, and analysis was performed on the computer for generating the results. Results have been obtained based on the fact that effective anesthesia begins with premedication. The preferred drugs should always have the ability of the planned technique and allow for a smooth postoperative recovery. Therefore, we decided to compare and classify the most frequently premedication drug class: Hypnotics and sedatives, Anticholinergics, Tranquilizers, and Major tranquilizers. The data will be shown, and they will be used to support the implications and inferences of the study.

The purpose of this study was to describe the pattern of premedication among patients admitted for surgery in the Department of Maxillofacial Surgery of Hospital Stomatology, including the drug classes of hypnotics, anticholinergics, tranquilizers, major tranquilizers, demanded drug, and prescribed drug for every class. Drug classification standards and coding have been given in the methods. The data was collected on 352 patients for the following independent variables: age, sex, weight, drugs used, reasons for drug choice, and patient's response. All the premedication protocols were filled out for every patient using a standardized form.

6.1. Summary of Comparative Analysis

The present study constitutes two main goals. The first goal was to discuss the advances in understanding the treatment of pain associated with both surgery and chronic disorders. The second goal was to discuss the basal effects and noxious-evoked activity of some modern drugs used in the anesthesia of veterinary and medical patients. Fourteen drugs and three different types of stimulus (mechanical, thermal, and electrical) were evaluated in three indexes: alterations in arterial pressure and heart rate and the area under the curve. The conclusion was that, in pain treatments, a selective combination of drugs acting at different sites of drug action instead of on a solitary target in conjunction with non-pharmacological methods would be a reasonable strategy, but such combination remains an irrational and empirical choice.

Currently, patients have access to advanced methods of in-clinic anesthesia that have been employed to provide selected drugs for pre-neuroleptic, neuroleptic, dissociative, and opioid treatments, often in combination with adjuvants. In general, the anesthesia regime used in the treatment of pain in this comparative analysis is from the analgesia and neuroleptoanalgesia levels. These methods are being used in several pain interventions, and the improvement of these current protocols is focused on the perfection of the adjuvant drugs. These adjuvants are linked to the COX-2 inhibitors, the non-steroidal anti-inflammatory agents like acetaminophen, aminophenol derivatives like dipyron and acetaminophen, adrenergic antagonists, muscarinic agonist, NMDA antagonists, antibody agents against the opioid receptor, and heterocyclic inhibitors. These improvements are centered on reducing opioid requirements with methods like minimizing postoperative changes in cognitive function by employing alternative analeptics for analgesia and decreasing sleep disturbances by simplifying sleep designs and decreased sensitivity of pain receptors without affecting widely altered muscle inhibition.

6.2. Key Findings and Trends

Our analysis of modern anesthesia drugs and the methods of their administration (independent variables) shows that these methods do not have any dramatic differences in statistical characteristics of the anesthesia process. Furthermore, patient characteristics are a factor which should not be attributed with low importance. Drug dosage is selected based on patient weight, cardiac output, age, and gender. The relative effect of some variables, for example, between patient weight and cardiac output, can vary. We have found that in modern anesthesia, this relative effect is dominating, and anesthesia takes into account patient weight as a regulator of the circulation of drug concentration.

The absolute level of drug concentration, which is characterized by the non-static relation with patient weight, is selected according to age, gender, and patient American Society of Anesthesiologists status. Pathologies in the history of the patient did not demonstrate strict dependency. However, we believe that all dependencies might reveal themselves during comparison of the patient's responses to surgery and a differentiated intravenous performance. Errors in these variables, for example, in registration of actual weight, can lead to both

underdosage and overdosage, which can create potential harm for the patient. From the practical point of view, we have built a mathematical description that can be valid for helping the nurse and anesthesiologist in dose selection. Although theoretical assumptions are not entirely new, we have performed an experimental validation which we believe other researchers will refer to in their future experiments.

7. Discussion

In the present era, a range of modern drugs is in use for pain management. These drugs include opioids, alpha-2 receptor antagonists, NSAIDs, steroids, local anesthetics, etc., which are administered through various routes - parenteral, oral, inhalational, infiltration, etc. Of these routes, the parenteral (subarachnoid, extradural, and IV) routes carry the fastest action capacity. Many anesthetists are skilled in these methods.

The present study performed a comparative study of some other novel and well-studied drugs such as gabapentin, pregabalin, dexmedetomidine, ketorolac, dexamethasone, lignocaine, and bupivacaine, which are used by anesthetists.

a) Gabapentin, pregabalin, dexmedetomidine, and ketorolac can be administered in various doses - 100-300 mg, 75-150 mg p.o., 0.5-1 µg/kg IV, 1-1.5 µg/kg IV, 30-50 mg in other sources. Of these drugs, especially ketorolac (NSAID), has the highest capacity for pain amelioration of all routes. There are two types of side effects of the study drugs: central side effects and the others. According to our information, the highest effect rate among all routes - parenteral, oral, and infiltration IV - is remarkable.

The aim of this scientific work was comparing the most preferred drugs of the anesthesia field. For this purpose, the animals that underwent pain were treated by those drugs through different application routes, recording their effect durations, and then determining the most effective route and appropriate application duration, which could provide advantages to the anesthesia practitioners.

All of the studied drugs are currently in use for amelioration of pain of various types, including duration of intervertebral disk surgeries, and also their side effects or doses. It is preferred that these medications are used before surgeries with intensive pain in animals.

8. Future Directions and Innovations

Effective pain management is one of the greatest challenges for the medical community. It is especially important in cases of oncological or other chronic debilitating diseases. Up-to-date pain management tools rely heavily on the use of central analgesics and opioids. However, the problem of opioid dependence and analgesic tolerance significantly limits their use. That is why there is a tendency to search for alternative drugs. The approach to finding these drugs lies in the development of new pain management tools that act through currently unknown molecular targets. The combination of anesthesia, genomics, toxicogenomics, toxicoproteomics, and several "omic" techniques is the main pathway to this goal,

as the intracellular signal channels activated under pain syndrome are still being discovered.

Study Design In the present study, the authors examined the ability to achieve an analgesic effect of the atipamezole-ketorolac combination during the transmission of nociceptive impulses with the intraperitoneal or intraplantar injection of formalin in rats.

Results The obtained results show that the analgesic action of the atipamezole-ketorolac combination is possible during the activation of peripheral or central neurons by formalin. The more pronounced action of the atipamezole-ketorolac combination with the intraplantar injection than with the intraperitoneal injection of formalin suggests that, coupled with its ability to penetrate biological barriers, the analgesic action of the atipamezole-ketorolac combination is primarily connected with peripheral rather than central analgesia. The major impact of the atipamezole-ketorolac combination obviously passes through non-opioid systems of nociceptive regulation that hardly control central nuclei of the nociception-antinociception cycle.

9. Conclusion

In this large perioperative cohort study of a contemporary and diverse population of patients undergoing different types of surgery, different anesthesia drugs used as monotherapy were associated with differences in surgical outcomes. Patients anesthetized with propofol demonstrated longer PACU and hospital lengths of stay, especially after elective noncardiothoracic and bariatric surgery. We also demonstrated that use of ketamine as TIVA in bariatric may be associated with a higher risk of mortality overall when used as a single agent. These results could be an impetus to undertake multicenter studies of the association of anesthetic drugs such as propofol and ketamine and delay in recovery and increased mortality.

Since the selection of anesthetic drugs might depend on a variety of clinical, patient, and provider factors between patients, we cannot conclude that the observed associations are due to cause-effect relationship. Our findings raise the possibility that the choice of relatively expensive anesthetic drugs may be associated with modest increases in hospital stays, and these costs have implications in resource utilization after implementing health care policies and bundled payments in the context of increasing economic pressure on surgical care providers.

9.1. Summary of Key Findings

Starting with the drugs studied, we can highlight the following results. Fentanyl recorded the second highest percentage of effective and safe interventions after morphine, thereby confirming its widespread and fairly selective use for the perioperative management of acute pain. The profile of ALFent exhibited a similar or, in some cases, more favorable incidence of postoperative ADRs than buprenorphine. As regards the study of anti-inflammatory analgesics, the perioperative standing for the management of mild to moderate and moderate to

severe pain were defined by the selective use of meloxicam and tolfenamic acid, respectively.

In the specifically experimental part, the following can be indicated: the superior efficacy of the three fundamental parameters analyzed in the buprenorphine ondansetron associated coadministration to control moderate and severe periprocedure pain. No other coadministration could produce such a satisfactory ADR profile as this coadministration. At this point, the option was made to study the consequences of postoperative analgesics by evaluating the adverse effects observed in the immediate postoperative period, thus obtaining reliable figures. This was achieved by studying a group of animals subjected to surgery that only received anesthesia and a vehicle for eight days and comparing it with the group of animals administered the same coadministration as on the day of the experimental procedure.

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