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COMPARISON OF MIDAZOLAM PREMEDICATION WITH PLACEBO ON HEMODYNAMICS IN FEMALES UNDERGOING HYSTERECTOMY UNDER GENERAL ANESTHESIA

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Abstract:

Background: *Hysterectomy is the surgical removal of the uterus. Hysterectomy, in the literal sense of the word, means merely removal of the uterus. Midazolam, is a medication used in general anesthesia, procedural sedation, trouble sleeping, and severe agitation. The goal of pre-medication is to have the patient arrive in the operating room in a calm, relaxed frame of mind. But controversies in literature have been noticed. So we conducted this study.*

Objective: *To compare the mean heart rate with midazolam premedication versus placebo in females undergoing hysterectomy under general anesthesia.*

Material & Methods:*This randomized control study was conducted at department of anesthesiology, Sir Ganga Ram Hospital, Lahore for 6 months (Date: from---to---). The non-probability consecutive sampling technique was used. Informed consent was obtained and demographics of patients were noted.*

The participants were randomly divided in two groups by using lottery method. Baseline heart rate was measured by using ECG monitor. Group M was given midazolam 2 ml (i.e 2 mg) and group C was given 2ml of physiological saline only, by a person not involved in taking observations. Then all patients followed-up till 15 minutes for assessment of heart rate. The data was entered and analyzed in SPSS version 20. Both groups were compared for mean heart rate by using t-test taking p-value≤ 0.05 as significant.

Results: *In our study the mean age of the patients was 48.11±10.30 years and the mean HR value at baseline of the patients was 88.25±11.31 per minute. Statistically there is highly significant difference was found between the study groups and the HR value at baseline i.e. p-value=0.000.*

HR value after 15 minutes in midazolam group was 80.03±9.917 per minute and its mean value in placebo group was 81.03±10.052 per minute and insignificant difference was found between the study groups. i.e p-value=0.437.

Conclusion: *Our study results concluded that there is insignificant difference was found the mean heart rate after 15 minutes with midazolam premedication versus placebo in females undergoing hysterectomy under general anesthesia*

Keywords: *Hysterectomy, Midazolam, General Anesthesia, Heart Rate, Beats per Minutes*

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INTRODUCTION:

General anesthesia uses intravenous and inhaled agents to allow adequate surgical access to the operative site. Anesthesia providers are responsible for assessing all factors that influence a patient's medical condition and selecting the optimal anesthetic technique accordingly.

Preoperative anxiety is a challenging concept in the preoperative care of patients and almost all patients undergoing surgery experience varying level ofanxiety [1].

Pre-medication is the first stage of a general anesthetic. Morphine and scopolamine were routinely administered to make the inhalation of highly pungent ether and chloroform vapors more tolerable. The goal of pre-medication is to have the patient arrive in the operating room in a calm, relaxed frame of mind. The most commonly used pre-medication is midazolam, a short-acting benzodiazepine [1].

It has been demonstrated that women undergoing invasive radiological or surgical procedures for gynaecological disorders experience higher levels of anxiety, express more worry, display greater heart rate and blood pressure changes before and during surgery, are more difficult to anaesthetize and are more likely to experience headache, vomiting and pain in postoperative period [3,4].

Pre-medication is expedient in reducing the psychological trauma from recalling the unpleasant pre-anesthetic phases, hence, inducing a trouble-free anesthesia [5] Midazolam is used as the pre-medication in more than 90% of surgical operations in the United State of America [2]. Intravenous midazolam reduces blood pressure and peripheral vascular resistance [7].

A recent study in 2014, found that the heart rate with midazolam was 73.60±12.341bpm (n=35) which was significantly lower as compared to placebo (79.06±10.218bpm, n=35). The reported difference was significant (P<0.05) [3].

But a recent study in 2014, found that the heart rate with midazolam was 73.60±12.341bpm (n=35) which was significantly lower as compared to placebo (79.06±10.218bpm, n=35). The reported difference was significant (P<0.05) [6].

Rationale of this study is to compare the mean heart rate with midazolam pre-medication versus control in females undergoing hysterectomy under general anesthesia. Development of abnormal hemodyanamics is common problem of general anesthesia. Midazolam is used to relieve anxiety and provide sedation. But in developing country like Pakistan, midazolam is not regularly practiced. Moreover, literature has reported controversial results regarding effect of midazolam on heart rate. Furthermore, no local evidence was found which can help us to implement the use of midazolam premedication to prevent abnormality of heart rate during general anesthesia. If lower heart rate is found with midazolam then it can be used in the future for the control of heart rate after anesthesia.

LITERATURE REVIEW:

Hysterectomy

Hysterectomy is the surgical removal of the uterus. It may also involve removal of the cervix, ovaries, fallopian tubes and other surrounding structures [4].

Usually performed by a gynecologist, hysterectomy may be total (removing the body, fundus, and cervix of the uterus; often called "complete") or partial (removal of the uterine body while leaving the cervix intact; also called "supracervical"). It is the most commonly performed gynecological surgical procedure. In 2003, over 600,000 hysterectomies were performed in the United States alone, of which over 90% were performed for benign conditions [4,5].

Such rates being highest in the industrialized world has led to the major controversy that hysterectomies are being largely performed for unwarranted and unnecessary reasons [5].

Removal of the uterus renders the patient unable to bear children (as does removal of ovaries and fallopian tubes) and has surgical risks as well as long-term effects, so the surgery is normally recommended when other treatment options are not available or have failed. It is expected that the frequency of hysterectomies for non-malignant indications will fall as there are good alternatives in many cases [6].

Oophorectomy (removal of ovaries) is frequently done together with hysterectomy to decrease the risk of ovarian cancer. However, recent studies have shown that prophylactic oophorectomy without an urgent medical indication decreases a woman's long-term survival rates substantially and has other serious adverse effects [7,8].

This effect is not limited to pre-menopausal women; even women who have already entered menopause were shown to have experienced a decrease in long-term survivability post-oophorectomy [9].

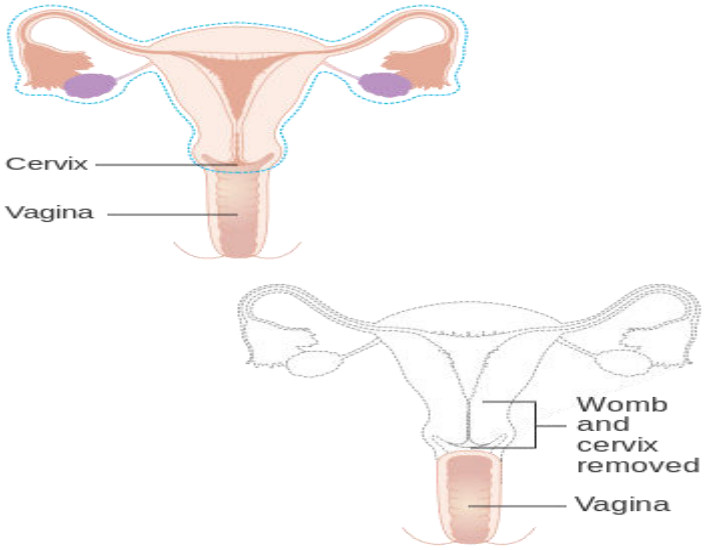

Fig i: Diagram showing what is removed with a radical hysterectomy [10]

Background of hysterectomy

Hysterectomy is the most common non–pregnancy-related major surgery performed on women in the United States. This surgical procedure involves removal of the uterus and cervix, and for some conditions, the fallopian tubes and ovaries [11].

Reasons for choosing this operation are treatment of uterine cancer and various common noncancerous uterine conditions such as fibroids, endometriosis, prolapse that leads to disabling levels of pain, discomfort, uterine bleeding, and emotional stress. [11].

Although this procedure is highly successful in curing the disease of concern, it is a surgical alternative with the accompanying risks, morbidity, and mortality that an operative procedure carries and it leads to sterility in women who are premenopausal. The patient may be hospitalized for several days and may require 6-12 weeks of convalescence. Complications, such as excessive bleeding, infection, and injury to adjacent organs, also may occur [11].

Epidemiology of hysterectomy

Canada

In Canada, the number of hysterectomies between 2008 and 2009 was almost 47,000. The national rate for the same timeline was 338 per 100,000 populations, down from 484 per 100,000 in 1997. The reasons for hysterectomies differed depending on whether the woman was living in an urban or rural location. Urban women opted for hysterectomies due to uterine fibroids and rural women had hysterectomies mostly for menstrual disorders [12].

United States

According to the National Center for Health Statistics, of the 617,000 hysterectomies performed in 2004, 73% also involved the surgical removal of the ovaries. In the United States, 1 in 3 women can be expected to have a hysterectomy by age 60. There are currently an estimated 22 million women in the United States who have undergone this procedure [13].

According to the same source, hysterectomy is the second most common major surgery among women in the United States (the first is cesaerean section). In the 1980s and 1990s, this statistic was the source of concern among some consumer rights groups and puzzlement among the medical community, and brought about informed choice advocacy groups like Hysterectomy Educational Resources and Services (HERS) Foundation, founded by Nora W. Coffey in 1982 [10].

United Kingdom

In the UK, 1 in 5 women are likely to have a hysterectomy by the age of 60, and ovaries are removed in about 20% of hysterectomies [14].

Germany

The number of hysterectomies in Germany has been constant for many years. In 2006, 149,456 hysterectomies were performed. Of these, 126,743 (84.8%) successfully benefitted the patient without incident. Women between the ages of 40 and 49 accounted for 50 percent of hysterectomies, and those between the ages of 50 and 59 accounted for 20 percent [15].

In 2007, the number of hysterectomies decreased to 138,164 [16]. In recent years, the technique of laparoscopic or laparoscopically assisted hysterectomies has been raised into the foreground [17,18].

Denmark
In Denmark, the number of hysterectomies from the 80s to the 90s decreased by 38%. In 1988, there were 173 such surgeries per 100,000 women, and by 1998 this number had been reduced to 107. The proportion of abdominal supracervical hysterectomies in the same time period grew from 7.5 to 41 percent. A total of 67,096 women underwent hysterectomy during these years [19].

Relevant Anatomy for hysterectomy
Various hysterectomy procedures are available, including the following:

- Total abdominal hysterectomy involves removal of the uterus and cervix through an abdominal incision [11].
- Supracervical or subtotal hysterectomy is removal of the uterus through an abdominal incision, while sparing the cervix [11].
- Radical hysterectomy is extensive surgery that, in addition to removal of the uterus and cervix, might include removal of lymph nodes, loose areolar tissue near major blood vessels, upper vagina, and omentum.[11]
- Oophorectomy and salpingo-oophorectomy: Oophorectomy is the surgical removal of the ovary and salpingo-oophorectomy is the removal of the ovary and the fallopian tube [11].
- Vaginal hysterectomy is removal of the uterus and the cervix through the vagina [11].
- Laparoscopy-assisted vaginal hysterectomy is vaginal hysterectomy with the help of laparoscopy [11].

The uterus is the inverted pear-shaped female reproductive organ that lies in the midline of the body, within the pelvis between the bladder and the rectum. It is a dynamic female reproductive organ that is responsible for several reproductive functions, including menses, implantation, gestation, labor, and delivery. It is responsive to the hormonal milieu within the body, which allows adaptation to the different stages of a woman's reproductive life. The uterus adjusts to reflect changes in ovarian steroid production during the menstrual cycle and displays rapid growth and specialized contractile activity during pregnancy and childbirth. It can also remain in a relatively quiescent state during the prepubertal and postmenopausal years [11].

The ovaries are small, oval-shaped, and grayish in color, with an uneven surface. The actual size of an ovary depends on a woman's age and hormonal status; the ovaries, covered by a modified peritoneum, are approximately 3-5 cm in length during childbearing years and become much smaller and then atrophic once menopause occurs. A cross-section of the ovary reveals many cystic structures that vary in size. These structures represent ovarian follicles at different stages of development and degeneration [11].

Medical uses of hysterectomy
Hysterectomy is a major surgical procedure that has risks and benefits, and affects a woman's hormonal balance and overall health for the rest of her life. Because of this, hysterectomy is normally recommended as a last resort to remedy certain intractable uterine/reproductive system conditions. Such conditions include, but are not limited to:[10]

Certain types of reproductive system cancers (uterine, cervical, ovarian, endometrium) or tumors, including uterine fibroids that do not respond to more conservative treatment options [10].
Severe and intractable endometriosis (growth of the uterine lining outside the uterine cavity) and/or adenomyosis (a form of endometriosis, where the uterine lining has grown into and sometimes through the uterine wall musculature), after pharmaceutical or other surgical options have been exhausted [10].
Chronic pelvic pain, after pharmaceutical or other surgical options have been exhausted [10].
Postpartum to remove either a severe case of placenta praevia (a placenta that has either formed over or inside the birth canal) or placenta percreta (a placenta that has grown into and through the wall of the uterus to attach itself to other organs), as well as a last resort in case of excessive obstetrical haemorrhage [20].
Several forms of vaginal prolapse [20].

Occasionally, women express a desire to undergo an elective hysterectomy—that is, a hysterectomy for reasons other than the resolution of reproductive system conditions or illnesses. Some of the conditions under which a person may request to have a hysterectomy (or have one requested for her if the woman is incapable of making the request) for non-illness reasons include [20]:

Prophylaxis against certain reproductive system cancers, especially if there is a strong family history of reproductive system cancers (especially breast cancer in conjunction with BRCA1 or BRCA2 mutation), or as part of recovery from such cancers.[20]
Part of overall gender transition for trans men [21].

Severe developmental disabilities, though this treatment is controversial at best. In the United States, specific cases of sterilization due to developmental disabilities have been found by state-level Supreme Courts to violate the patient's constitutional and common law rights [21].

Hysterectomies with bilateral salpingo-oophorectomy are often performed either prior to or as a part of sex reassignment surgery for trans men. Some in the FTM community prefer to have this operation along with hormone replacement therapy in the early stages of their gender transition to avoid complications from heavy testosterone use while still having female-hormone-producing organs in place (e.g. uterine cancer and hormonally induced coronary artery disease) or to remove as many sources of female sex hormones as possible in order to better "pass" during the real life experience portion of their transition. Just as many, however, prefer to wait until they have full "bottom surgery" (removal of female sexual organs and construction of male-appearing external anatomy) [22] to avoid undergoing multiple separate operations [22].

Risk of Nerve damage during hysterectomy

The bilateral inferior hypogastricplexa provide sympathetic and parasympathetic innervation to the lower pelvic viscera and are located in close proximity to the proximal vagina and distal rectum. During the course of hysterectomy, the pelvic plexus may be at risk of injury in several areas: at the division of the cardinal ligaments; at the blunt dissection of the bladder from the uterus; at the dissection of the paravaginal tissue [23]; and at the removal of the cervix [24].

The pelvic floor muscles, as well as urethral and anal sphincters, are also innervated by distal branches of the pudendal nerves, supplying motor and sensory innervations [24].

Damage to the distal branches of the pudendal nerves and the inferior hypogastricplexa may impede the intricate urethral sphincter closing mechanism and cause chronic or progressive denervation injury. This may eventually lead to the development of incontinence [25,26].

Posthysterectomy alterations in urethral innervation and anatomy may also give rise to changes in urethral pressure dynamics and bladder neck support, resulting in deterioration of urethral function [27]. However, stress urinary incontinence and urge urinary incontinence may have different pathophysiologies, as well as different predisposing risk factors [28].

The pathophysiological basis for bowel dysfunction after hysterectomy may involve changes in rectal support and dynamics. The pelvic plexus is of paramount importance in the coordinated contractions of the smooth muscle of the bowel [29], and nerve conductance impairment may result in bowel dysfunction and constipation.

Sharp or blunt severing of pelvic organ supportive tissues at the time of hysterectomy may interfere with the anorectal innervation, mainly the pudendal nerve, and provide the pathophysiologic basis for anal incontinence [29].

Types of hysterectomy

Hysterectomy, in the literal sense of the word, means merely removal of the uterus. However other organs such as ovaries, fallopian tubes and the cervix are very frequently removed as part of the surgery [30].

Radical hysterectomy: complete removal of the uterus, cervix, upper vagina, and parametrium. Indicated for cancer. Lymph nodes, ovaries and fallopian tubes are also usually removed in this situation, such as in Wertheim's hysterectomy. [30].

Total hysterectomy: complete removal of the uterus and cervix, with or without oophorectomy.

Subtotal hysterectomy: removal of the uterus, leaving the cervix in situ [30].

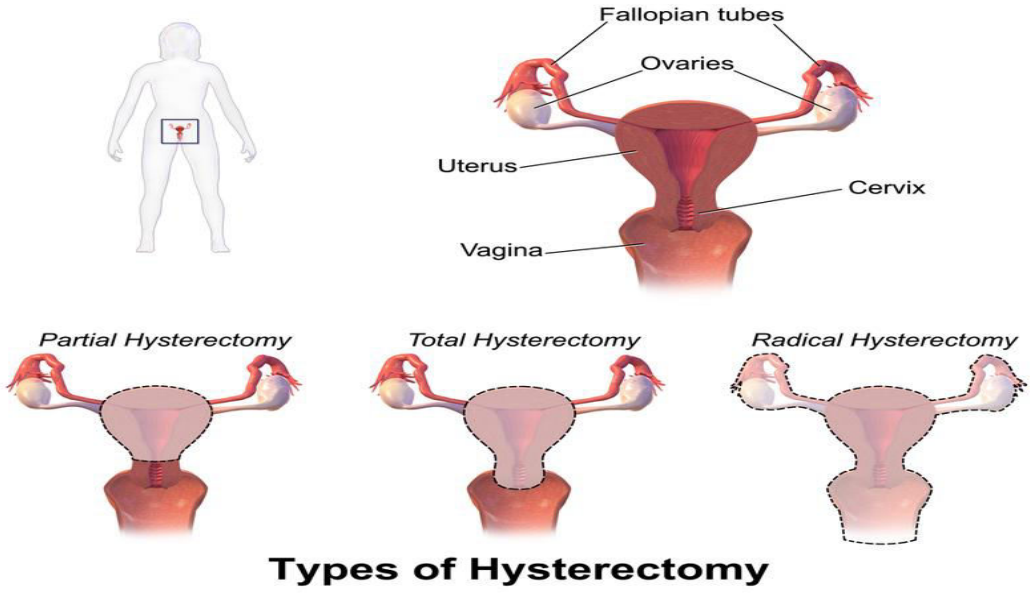

Fig ii: Transitioning from female-to-male [10]

Subtotal (supracervical) hysterectomy was originally proposed with the expectation that it may improve sexual functioning after hysterectomy, it has been postulated that removing the cervix causes excessive neurologic and anatomic disruption, thus leading to vaginal shortening, vaginal vault prolapse, and vaginal cuff granulations. These theoretical advantages were not confirmed in practice, but other advantages over total hysterectomy emerged. The principal disadvantage is that risk of cervical cancer is not eliminated and women may continue cyclical bleeding (although substantially less than before the surgery). These issues were addressed in a systematic review of total versus supracervical hysterectomy for benign gynecological conditions, which reported the following findings [30].

There was no difference in the rates of incontinence, constipation, measures of sexual function or alleviation of pre-surgery symptoms [30].

Length of surgery and amount of blood lost during surgery were significantly reduced during supracervical hysterectomy compared to total hysterectomy, but there was no difference in post-operative transfusion rates [30].

Febrile morbidity was less likely and ongoing cyclic vaginal bleeding one year after surgery was more likely after supracervical hysterectomy [30].

There was no difference in the rates of other complications, recovery from surgery, or readmission rates [30].

In the short-term, randomized trials have shown that cervical preservation or removal does not affect the rate of subsequent pelvic organ prolapse. [31].

Supracervical hysterectomy does not eliminate the possibility of having cervical cancer since the cervix itself is left intact and may be contraindicated in women with increased risk of this cancer, regular pap smears to check for cervical dysplasia or cancer are still needed [32,33].

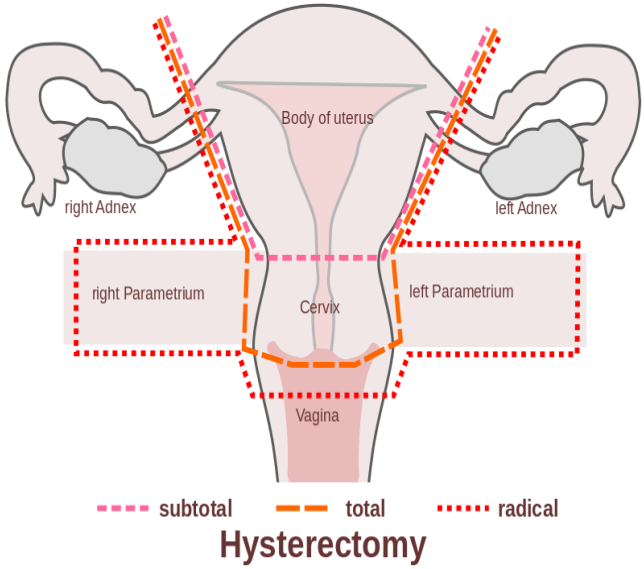

Fig iii: Schematic drawing of types of hysterectomy [10]

Application of hysterectomy

Although hysterectomy is often the definitive treatment for many pelvic pathologies, nonsurgical alternatives should always be attempted in elective cases [11]. Hormonal therapy, gonadotropin-releasing hormone antagonists, progesterone-containing IUD, endometrial ablation, focused ultrasonographic surgery, cryotherapy, and uterine artery embolization have been used with success [11].

In the 6 states studied, the diffusion of endometrial ablation has had a varying impact on hysterectomy rates among women with benign uterine conditions. However, endometrial ablation is used as an additive medical technology rather than a substitute [11].

General anesthesia

General anesthesia commences after intravenous boluses of hypnotic, paralytic, analgesic and amnestic drugs produce unconsciousness and loss of reflexes. During this period of profound, drug-induced obtundation, endotracheal intubation with a cuffed endotracheal tube or less frequently, a laryngeal mask airway (LMA) is performed. When proper airway placement is insured by bilateral equal breath sounds, presence of end tidal carbon dioxide (ETCO2) and an equally rising thorax, the tube is secured. The patient's eyes are lubricated with water-soluble ointment and covered with tape to protect them from corneal injury.

Manual "bagging" or mechanical ventilation via a gas machine suffuses mixtures of oxygen, nitrous oxide, and inhalational anesthetic agents, such as Forane, Sevoflurane, or Desflurane into the patient's lungs. Alternatively, total intravenous anesthesia (TIVA) can be induced without the use of inhalational anesthetic gases.

Intravenous injection of large doses of narcotics, benzodiazepines, and hypnotic agents cause

unconsciousness, amnesia and analgesia. Muscle relaxing drugs, which produce temporary paralysis of abdominal , thoracic, and pelvic musculature, further enhance surgical access for both inhalational and intravenous techniques [34].

Abdominal hysterectomy

In November 1843, Charles Clay performed the first hysterectomy in Manchester, England. The earliest hysterectomies were supracervical, or subtotal, hysterectomies. The body of the uterus was removed while the cervix remained intact. In 1929, Richardson, MD, performed the first TAH, in which the entire uterus was removed [35].

Prior to an abdominal hysterectomy, the patient undergoes a regional or general anesthetic. A patient remains awake during a regional anesthetic, with only part of the body being numbed to prevent pain. When given a general anesthetic, the patient is unconscious. In the absence of contraindications, neuraxial anesthesia provides a better quality of recovery than general anesthesia [36].

The abdominal hysterectomy begins via a surgical incision 6-8 inches long, made either vertically, running from the navel to the pubic bone, or horizontally, running along the top of the pubic hairline. The cut exposes the ligaments and blood vessels surrounding the uterus. These ligaments and blood vessels then are separated from the uterus and cervix. In the process, the blood vessels are tied off to prevent bleeding and to help in healing. The uterus and cervix are then cut off at the superior portion of the vagina and removed. The top of the vaginal cuff is closed with sutures, and the surgical wound is closed in layers [36].

An abdominal hysterectomy may be performed in conjunction with a salpingo-oophorectomy, in which the adnexa are removed, if needed. Possible complications include surgical wound infection; excessive bleeding; injury to the bowel, bladder, or ureter; nerve damage; and urinary tract infection. Candidates for this surgery include those who have fibroids, abnormal or heavy bleeding, chronic pelvic pain, endometriosis, adenomyosis (endometrial tissue that has infiltrated the myometrium), uterine prolapse, cancer of the reproductive organs, or pelvic inflammatory disease [36].

Vaginal hysterectomy

In a vaginal hysterectomy, the uterus is removed through the vaginal introitus. Prior to surgery, the patient is given a regional or a general anesthetic and the skin surrounding the vagina is prepped with an antibacterial solution. A surgical incision is then made in a circular fashion around the cervix and through the upper vagina to expose the tissue and blood vessels around the cervix and uterus. The tissues and vessels are cut and tied off for the uterus and cervix to be removed from the top of the vagina. The upper part of the vagina, where the surgical incision was made, is then sutured [36].

Possible complications include surgical wound infection; excessive bleeding; injury to the bowel, bladder, or ureter; nerve damage; and urinary tract infection. Often, colporrhaphy (reconstructive surgery) is performed to repair or prevent cystocele, rectocele, and/or vaginal vault prolapse [36].

Candidates for this surgery include those who have fibroids, abnormal or heavy bleeding, adenomyosis, uterine prolapse, early-stage cancer of the reproductive organs, or precancerous conditions of reproductive organs.[36]

Laparoscopically assisted vaginal hysterectomy

Laparoscopically assisted vaginal hysterectomy (LAVH) is a procedure that uses laparoscopic surgical techniques and instruments to remove the uterus, cervix, and/or fallopian tubes and ovaries through the vagina. Prior to surgery, the patient is usually given a general anesthetic and the abdomen and vagina are prepared with an antibacterial solution [36].

LAVH begins with several small abdominal incisions inferior to the belly button, which allow the insertion of the laparoscope and other surgical tools. In order for the surgeon to observe the inside of the body clearly, the peritoneal cavity is inflated with gas (usually carbon dioxide), and a camera, which is attached to the laparoscope, captures and produces a continuous image that is magnified and projected onto a television screen [36].

Using the laparoscopic surgical tools, the tissues and vessels surrounding the uterus are cut and tied off. The uterus and cervix are then removed through the vagina, and the top of the vaginal cuff is sutured. The fallopian tubes and ovaries also may be removed during this surgical procedure[36].

Possible complications include surgical wound infection; excessive bleeding; injury to the bowel, bladder, or ureter; nerve damage; and urinary tract infection. Candidates for this surgery include those who have had previous abdominal surgery, large fibroids, chronic pelvic pain, endometriosis, or pelvic inflammatory disease, or those who want an oophorectomy. Today, robotic laparoscopic surgery, such as procedures involving the da Vinci Surgical Robot, is also being refined to evaluate the performance of LAVH[36].

Laparoscopic hysterectomy

Laparoscopic hysterectomy (LH) is a procedure in which the uterus and cervix are dissected and ligated from ligaments, tissues, vagina, and blood vessels and removed entirely from small abdominal incisions with the help of instruments like the morcellator. This procedure requires good surgical technique, intra and extracorporal sutures, and different hemostatic devices[37].

A meta-analysis showed no difference between total LH and vaginal hysterectomy for benign

disease in perioperative complications. Total LH was associated with lower pain scores and reduced hospital stay but took longer to perform[37].

Supracervical hysterectomy

Supracervical hysterectomy is defined as removal of the uterine corpus with preservation of the cervix and can be performed through abdominal, laparoscopic, or robotic approaches [37].

During supracervical hysterectomy, removal of the corpus is at or below the internal os along with ablation of the endocervical canal. During laparoscopic and robotically assisted hysterectomy, morcellation of the uterine fundus is performed to facilitate its removal through the port site incisions [37].

Women with known or suspected gynecological cancer, current or recent cervical dysplasia, or endometrial hyperplasia are not candidates for a supracervical procedure [37].

Evidence regarding the potential benefits of this procedure like less blood loss, shorter operating time, and fewer complications are limited to retrospective series. Patients should be counseled about the need for long-term follow up, the possibility of future trachelectomy, and the lack of data demonstrating clear benefits over total hysterectomy; hence, it should not be recommended by the surgeon as a superior technique for hysterectomy for benign diseases [38].

Robot-assisted hysterectomy

Da Vinci surgical system was approved for use in gynecological surgery by FDA in 2005.[38].

Da Vinci hysterectomy involves a robotic system in which the surgeon's hands are naturally positioned while his or her fingers grasp the controls below the display, and movements are transferred in real time to surgical instruments inside the patient. This system is useful when the surgery involves dissection in a difficult situation, such as near the ureters, bladder, or blood vessels [38].

The current system consists of 4 components: (1) console where the surgeon sits and views the screen and controls the robotic instruments, (2) robotic cart with interactive arms, (3) camera and vision system, (4) wristed instruments with computer interfaces [38].

Advantages are 3-dimensional visualization with improved depth of perception, improved dexterity, less blood loss, shorter hospital stay, less pain, and less risk of wound infection[39].

Disadvantages include high cost, increased operating time associated with set up and docking, lack of tactile feedback, inability to reposition the patient once the robotic arms are attached, and the bulkiness of the system.[39]

Comparisons of hysterectomy procedures

With the various hysterectomy procedures available, physicians must limit healthcare dollars associated with these surgical procedures while maintaining quality health care for patients. Various studies have been performed to decide which surgical procedure is most suitable in terms of economics and patient health.[40]

The severity of the pathological disorder must be the key standard in selecting the type of hysterectomy, in order to maintain optimum surgical practice. In studies performed in the United States, France, and the United Kingdom in which strict guidelines based on the severity of the pathological disorder have been implemented, most patients underwent successful vaginal hysterectomy without abdominal or laparoscopic assistance [40].

In a study by Gimbel et al subtotal hysterectomy is faster to perform, has less perioperative bleeding, and seems to have less intra- and postoperative complications. However it does have a slightly high rate of urinary incontinence and cervical stump problems [41].

Significantly improved outcomes suggest vaginal hysterectomy (VH) should be performed in preference to abdominal hysterectomy (AH) where possible. Where VH is not possible, LH may avoid the need for AH; however, the length of the surgery increases as the extent of the surgery performed laparoscopically increases, particularly when the uterine arteries are divided laparoscopically. Also, laparoscopic approaches require greater surgical expertise [42].

Four-year follow-up data indicate that patients who underwent laparoscopic hysterectomy reported a better quality of life compared to those who underwent AH.[43].

Laparoscopic hysterectomy should be considered for patients in whom VH is not possible[43].

Postoperative Details

Early feeding (oral intake of fluids or food within 24 h of surgery, irrespective of bowel sounds) after major abdominal gynecological surgery is safe and associated with reduced length of hospital stay but increased nausea. Further studies should focus on the cost effectiveness, patient satisfaction, and other physiological changes[44].

General Anesthesia?

General anaesthesia (or general anesthesia) is a medically induced coma and loss of protective reflexes resulting from the administration of one or more general anaesthetic agents. A variety of medications may be administered, with the overall aim of ensuring sleep, amnesia, analgesia, relaxation of skeletal muscles, and loss of control of reflexes of the autonomic nervous system. The optimal combination of these agents for any given patient and procedure is typically selected by an anaesthesiologist or another provider such as an anaesthesiologist assistant or nurse anaesthetist, in consultation with the patient and the medical or dental practitioner performing the operative procedure[45].

Stages of General Anesthesia

The Guedel's classification by Arthur Ernest Guedel described four stages of anaesthesia in 1937. Despite newer anaesthetic agents and delivery techniques, which have led to more rapid onset and recovery from anaesthesia, with greater safety margins, the principles remain.[46].

Stage 1

Stage 1 anaesthesia, also known as the "induction", is the period between the initial administration of the induction agents and loss of consciousness. During this stage, the patient progresses from analgesia without amnesia to analgesia with amnesia. Patients can carry on a conversation at this time [46].

Stage 2

Stage 2 anaesthesia, also known as the "excitement stage", is the period following loss of consciousness and marked by excited and delirious activity. During this stage, respirations and heart rate may become irregular. In addition, there may be uncontrolled movements, vomiting, breath holding, and pupillary dilation. Since the combination of spastic movements, vomiting, and irregular respirations may lead to airway compromise, rapidly acting drugs are used to minimize time in this stage and reach stage 3 as fast as possible [46].

Stage 3

Stage 3, "surgical anaesthesia". During this stage, the skeletal muscles relax, vomiting stops, and respiratory depression occurs . Eye movements slow, then stop, the patient is unconscious and ready for surgery. It has been divided into 4 planes:

- eyes initially rolling, then becoming fixed
- loss of corneal and laryngeal reflexes
- pupils dilate and loss of light reflex
- intercostal paralysis, shallow abdominal respiration [46].

Stage 4

Stage 4 anaesthesia, also known as "overdose", is the stage where too much medication has been given relative to the amount of surgical stimulation and the patient has severe brain stem or medullary depression. This results in a cessation of respiration and potential cardiovascular collapse. This stage is lethal without cardiovascular and respiratory support.[46].

Physiologic Monitoringof General Anesthesia

Monitoring involves the use of several technologies to allow for a controlled induction of, maintenance of and emergence from general anaesthesia.

1. Continuous Electrocardiography (ECG): The placement of electrodes that monitor heart rate and rhythm. This may also help the anaesthetist to identify early signs of heart ischaemia.
2. Continuous pulse oximetry (SpO2): The placement of this device (usually on one of the fingers) allows for early detection of a fall in a patient's haemoglobin saturation with oxygen (hypoxaemia).
3. Blood Pressure Monitoring (NIBP or IBP): There are two methods of measuring the patient's blood pressure. The first, and most common, is called non-invasive blood pressure (NIBP) monitoring. This involves placing a blood pressure cuff around the patient's arm, forearm or leg. A blood pressure machine takes blood pressure readings at regular, preset intervals throughout the surgery. The second method is called invasive blood pressure (IBP) monitoring. This method is reserved for patients with significant heart or lung disease, the critically ill, major surgery such as cardiac or transplant surgery, or when large blood losses are expected. The invasive blood pressure monitoring technique involves placing a special type of plastic cannula in the patient's artery - usually at the wrist or in the groin.[45]
4. Agent concentration measurement - Common anaesthetic machines have monitors to measure the per cent of inhalational anaesthetic agent used (e.g. sevoflurane, isoflurane, desflurane, halothane etc.). The monitors also usually measure nitrous oxide and oxygen percentages and could give a MAC level.
5. Low oxygen alarm - Almost all circuits have a backup alarm in case the oxygen delivery to the patient becomes compromised. This warns if the fraction of inspired oxygen drops lower than minimum alarm setting and allows the anaesthetist to take immediate remedial action.
6. Circuit-disconnect alarm or low pressure alarm indicates failure of circuit to achieve a given pressure during mechanical ventilation.
7. Carbon dioxide measurement (capnography)- measures the amount of carbon dioxide expired by the patient's lungs in per cent or mmHg, mmHg is usually used to allow the anaesthesia provider to see more subtle changes in CO2. It allows the anaesthetist to assess the adequacy of ventilation
8. Temperature measurement to discern hypothermia or fever, and to aid early detection of malignant hyperthermia.
9. EEG or other system to verify depth of anaesthesia may also be used. This reduces the likelihood that a patient will be mentally awake, although unable to move because of the paralytic agents. It also reduces the likelihood of a patient receiving significantly more amnesic drugs than actually necessary to do the job[45].

Airway management

With the loss of consciousness caused by general anaesthesia, there is loss of protective airway reflexes (such as coughing), loss of airway patency and sometimes loss of a regular breathing pattern due to the effect of anaesthetics, opioids, or muscle relaxants. To maintain an open airway and regulate breathing within acceptable parameters, some form of "breathing tube" is inserted in the airway after the patient is unconscious. To enable mechanical ventilation, an endotracheal tube is often used (intubation), although there are alternative devices such as face masks or laryngeal mask airways [45].

Eye management

General anaesthesia reduces the tonic contraction of the orbicularis oculi muscle, causing lagophthalmos, or incomplete eye closure in 59% of patients. In addition, tear production and tear-film stability are reduced, resulting in corneal epithelial drying and reduced lysosomal protection. The protection afforded by Bell's phenomenon (in which the eyeball turns upwards during sleep, protecting the cornea) is also lost during general anaesthesia. Careful eye management is required, to reduce the likelihood of eye injuries during general anaesthesia[47,48].

Neuromuscular blockade

"Paralysis" or temporary muscle relaxation with a neuromuscular blocker is an integral part of modern anaesthesia. The first drug used for this purpose was curare, introduced in the 1940s, which has now been superseded by drugs with fewer side effects and generally shorter duration of action. Muscle relaxation allows surgery within major body cavities, e.g. abdomen and thorax without the need for very deep anaesthesia, and is also used to facilitate endotracheal intubation. Acetylcholine, the natural neurotransmitter substance at the neuromuscular junction, causes muscles to contract when it is released from nerve endings. Muscle relaxants work by preventing acetylcholine from attaching to its receptor. Paralysis of the muscles of respiration, i.e. the diaphragm and intercostal muscles of the chest requires that some form of artificial respiration be implemented. As the muscles of the larynx are also paralysed, the airway usually needs to be protected by means of an endotracheal tube. Monitoring of paralysis is most easily provided by means of a peripheral nerve stimulator. This device intermittently sends short electrical pulses through the skin over a peripheral nerve while the contraction of a muscle supplied by that nerve is observed. The effects of muscle relaxants are commonly reversed at the termination of surgery by anticholinesterase drugs. Examples of skeletal muscle relaxants in use today are pancuronium, rocuronium, vecuronium, atracurium, mivacurium, and succinylcholine[48].

Midazolam

Midazolam, marketed under the trade names Versed among others, is a medication used for anesthesia, procedural sedation, trouble sleeping, and severe agitation. It works by making people sleepy, decreasing anxiety, and causing a loss of ability to create new memories. It is also useful for the treatment of seizures.

Midazolam can be given by mouth, intravenously, by injection into a muscle, sprayed into the nose, or in the cheek. When given intravenously it begins working typically within five minutes, when injected into a muscle it can take fifteen minutes to begin working. Effects last for between one and six hours [49].

Side effects can include a decrease in efforts to breathe, low blood pressure, and sleepiness. Tolerance to its effects and withdrawal syndrome may occur following long term use. Paradoxical effects, such as increased activity, can occur especially in children and older people.

There is evidence of risk when used during pregnancy but no evidence of harm with a single dose during breastfeeding. It is of the benzodiazepine class and works through the GABA neurotransmitter [49].

Midazolam first came into use in 1976. It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system. Midazolam is available as a generic medication and is not very expensive. Wholesale a vial is about 0.35 USD. In many countries it is a controlled substance [49].

History of midazolam

Midazolam is among about 35 benzodiazepines which are currently used medically, and was synthesised in 1975 by Walser and Fryer at Hoffmann-LaRoche, Inc in the United States [50]. Owing to its water solubility, it was found to be less likely to cause thrombophlebitis than similar drugs [51]. The anticonvulsant properties of midazolam were studied in the late 1970s, but not until the 1990s did it emerge as an effective treatment for convulsive status epilepticus [52]. As of 2010, it is the most commonly used benzodiazepine in anesthetic medicine [53]. In acute medicine, midazolam has become more popular than other benzodiazepines, such as lorazepam and diazepam, because it is shorter lasting, is more potent, and causes less pain at the injection site [54]. Midazolam is also becoming increasingly popular in veterinary medicine due to its water solubility [55].

Medical uses of midazolam

Seizures

Midazolam is sometimes used for the acute management of seizures. Long-term use for the management of epilepsy is not recommended,

however, due to the significant risk of tolerance (which renders midazolam and other benzodiazepines ineffective) and the significant side effect of sedation. A benefit of midazolam is that in children it can be administered buccally or intranasally at home or at school for emergency control of acute seizures, including status epilepticus. Midazolam is effective for status epilepticus that has not improved following other treatments, and has advantages of being water-soluble, having a rapid onset of action and not causing metabolic acidosis from the propylene glycol vehicle, which occurs with other benzodiazepines. Drawbacks include a high degree of breakthrough seizures due to the short half-life of midazolam in over 50% of people treated, as well as treatment failure in 14–18% of people with refractory status epilepticus. Tolerance develops rapidly to the anticonvulsant effect, and the dose may need to be increased by several times to maintain anticonvulsant therapeutic effects. With prolonged use, tolerance and tachyphylaxis can occur and the elimination half-life may increase, up to days.There is evidence buccal and intranasal midazolam is easier to administer and more effective than rectally administered diazepam in the emergency control of seizures [49].

Procedural sedation

Intravenous midazolam is indicated for procedural sedation (often in combination with an opioid, such as fentanyl), for preoperative sedation, for the induction of general anesthesia, and for sedation of people who are ventilated in critical care units. Midazolam is superior to diazepam in impairing memory of endoscopy procedures, but propofol has a quicker recovery time and a better memory-impairing effect.

It is the most popular benzodiazepine in the intensive care unit (ICU) because of its short elimination half-life, combined with its water solubility and its suitability for continuous infusion. However, for long-term sedation, lorazepam is preferred due to its long duration of action, and propofol has advantages over midazolam when used in the ICU for sedation, such as shorter weaning time and earlier tracheal extubation [49].

Midazolam is sometimes used in neonatal intensive care units. When used, additional caution is required in newborns; midazolam should not be used for longer than 72 hours due to risks of tachyphylaxis, and the possibility of development of a benzodiazepine withdrawal syndrome, as well as neurological complications. Bolus injections should be avoided due to the increased risk of cardiovascular depression, as well as neurological complications. Midazolam is also sometimes used in newborns who are receiving mechanical ventilation, although morphine is preferred, owing to its better safety profile for this indication [49].

Problems sleeping

Oral midazolam is indicated for the short-term treatment of moderately severe insomnia in people who have not reacted adequately to other hypnotics, and who have persistent trouble in falling asleep. Because of midazolam's extremely short duration, it is not used for people who have trouble staying asleep through the night; moderate- to long-acting benzodiazepines, such as temazepam, nitrazepam, flunitrazepam, and lormetazepam, are used for those purposes. Midazolam and other benzodiazepines may cause deterioration in sleep quality [49].

Agitation

Midazolam in combination with an antipsychotic drug is indicated for the acute management of schizophrenia when it is associated with aggressive or out-of-control behaviour [49].

End of life care

In the final stages of end-of-life care, midazolam is routinely used at low doses via subcutaneous injection to help with agitation, myoclonus, restlessness or anxiety in the last hours or days of life. At higher doses during the last weeks of life, midazolam is considered a first line agent in palliative continuous deep sedation therapy when it is necessary to alleviate intolerable suffering not responsive to other treatments, but the need for this is rare [49].

Pharmacokinetics of midazolam

Midazolam is a short-acting benzodiazepine in adults with an elimination half-life of one to four hours; however, in the elderly, as well as young children and adolescents, the elimination half-life is longer.[56] Midazolam is metabolized into an active metabolite alpha1-hydroxymidazolam. Age-related deficits, renal and liver status affect the pharmacokinetic factors of midazolam as well as its active metabolite. However, the active metabolite of midazolam is minor and contributes to only 10 percent of biological activity of midazolam. Midazolam is poorly absorbed orally, with only 50 percent of the drug reaching the bloodstream [57].

Midazolam is metabolised by cytochrome P450 (CYP) enzymes and by glucuronide conjugation. The therapeutic as well as adverse effects of midazolam are due to its effects on the GABAA receptors; midazolam does not activate GABAA receptors directly but, as with other benzodiazepines, it enhances the effect of the neurotransmitter GABA on the GABAA receptors resulting in neural inhibition. Almost all of the properties can be explained by the actions of benzodiazepines on GABAA receptors. This results in the following pharmacological properties being produced: sedation, hypnotic, anxiolytic, anterograde amnesia, muscle relaxation and anti-convulsant [58].

How to use midazolam

Use midazolam as directed by doctor. Check the label on the medicine for exact dosing instructions [59].
Midazolam is usually administered as an injection at your doctor's office, clinic, or hospital. Ask doctor or pharmacist any questions that may have about midazolam [59].
If midazolam contains particles or is discolored, or if the vial is cracked or damaged in any way, do not use it. [59]
Keep this product, as well as syringes and needles, out of the reach of children and away from pets. Do not reuse needles, syringes, or other materials. Dispose of properly after use. Ask doctor or pharmacist to explain local regulations for proper disposal [59].
If miss a dose of midazolam, contact doctor immediately [59].
Ask health care provider any questions you may have about how to use midazolam [59].

Midazolam mechanism of action

The molecular mechanisms underlying the diverse actions remain unclear, although some of the midazolam mechanism of action and sites of action of benzodiazepines effects are known [60].
Benzodiazepines appear to produce all their pharmacologic effects by facilitating the actions of gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS [60]. Benzodiazepines do not activate the GABAA receptors but rather enhance the affinity of the receptors for GABA, as a result of which, there is enhanced opening of chloride gating channels resulting in increased chloride conductance [60].
This is turn produce hyperpolarization of the postsynaptic cell membrane, while rendering postsynaptic neurons more resistant to excitation, and midazolam mechanism of action.[60] This resistance to excitation is presumed to be the mechanism by which benzodiazepines produce anxiolysis, sedation, anterograde amnesia, alcohol potentiation and anticonvulsant and skeletal muscle relaxant effects, even seen with midazolam mechanism of action [60].
Midazolam mechanism of action is due to activation of alpha-1 subunits of GABA-A receptors whereas anxiolytic effect is due to alpha-2 subunit activity. Alpha-1 containing GABAA receptors are the most numerous accounting for 60% [60].
Alpha-2 subtypes are less common and present in hippocampus and amygdala. GABAA receptors are large macromolecules and provide separate attachment sites for GABA, benzodiazepines, barbiturates, etomidate, propofol, midazolam mechanism of action , neurosteroids and alcohol [60].
Acting on single receptors by different mechanisms, the benzodiazepines, barbiturates and alcohol can produce synergistic effects to increase GABAA receptor mediated inhibition in the CNS [60].
This synergy is also the basis of cross tolerance between different classes of drugs. Benzodiazepines decrease adenosine degradation by inhibiting nucleoside transporter.[60] Adenosine is an important regulator of cardiac function and its physiologic effects convey cardiac protection during myocardial ischaemia [60].
Midazolam mechanism of action given by intrathecal or epidural injection can produce antinociceptive effect. This could be GABA-mediated, because GABA has been shown to have analgesic properties, though its analgesic property is not as potent as opioids [60].

Sedative and cardiovascular effects of midazolam

Clonidine reduces the sympathetic activity and increases the parasympathetic activity, thus consequently reducing heart rate (HR), systemic metabolism, myocardial contractility, and systemic vascular resistance. All these effects result in a lower myocardial oxygen requirement, an aspect that should be considered in patients with coronary heart diseas [61].
Control of the autonomic response in patients with suspected coronary artery disease is already performed with the use of beta-blockers, whose efficacy is well known3. Alpha-2 agonists such as clonidine have been studied and their benefits on the autonomic control are evident [61].
Few studies on sedation during coronary angiography are available, and data on the use of alpha-2 agonists are particularly poor. Thus, the objective of this study was to evaluate the effects of clonidine, and to compare it to two benzodiazepines (midazolam and diazepam), and their combination, observing their effects on blood pressure (BP), HR, and sedation in patients undergoing coronary angiography [61].

Possible side effects of midazolam

All medicines may cause side effects, but many people have no, or minor, side effects. Check with doctor if any of these most common side effects persist or become bothersome [59]:
Blurred vision; changes in blood pressure, breathing, and heartbeats; coughing; dizziness; drowsiness; dry mouth; headache; hiccups; low blood pressure(children); nausea; pain during injection; pain, redness, or tenderness at the injection site; short-term memory loss; slurred speech; vomiting [59].
Seek medical attention right away if any of these severe side effects occur [59].
Severe allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); agitation; chest pain; combativeness; irregular breathing patterns; pain, swelling, or redness at the injection site; slow or

difficult breathing; unusual or involuntary muscle movements or muscle tremor [59].

THIS STUDY

OBJECTIVE:

To compare the mean heart rate with midazolam premedication versus placebo in females undergoing hysterectomy under general anesthesia.

Operational Definitions

Heart Rate

It was measured in beats per minute at the time of induction and 15 minutes after pre-medication with midazolam or placebo. It was measured by using ECG monitor.

Hypothesis:

There is a difference in mean heart rate with midazolam and placebo in females undergoing hysterectomy under general anesthesia**.**

MATERIALS AND METHODS:

Study Design

Randomized Control study

Setting

Department of Anesthesiology, Sir Ganga Ram Hospital, Lahore

Duration of Study

Six months after approval of synopsis.

Sample Size

Sample size of 140 cases; 70 cases in each group is calculated by using 95% confidence level, 80% power of test and taking magnitude of heart rate i.e.73.60±12.341 bpm[9] with midazolam and 79.06±10.218 bpm[9] without midazolam in females undergoing hysterectomy under general anesthesia.

Sampling Technique

Non probability consecutive sampling

Sampling Criteria

Inclusion Criteria:

- Patients of age 30-60 years undergoing hysterectomy under general anesthesia.
- Elective cases.
- ASA I & II patients (annexure)

Exclusion Criteria:

- Patients with deranged RFTs (creatinine>1.2mg/dl), deranged LFTs (AST>40IU, ALT>40IU)
- Hypertensive cases (BP≥140/90mmHg), cardiac problems (abnormal ECG, heart rate<60/min or >100/min before surgery), medical record of CABG or arrhythmias.
- Diabetes (BSR>126mg/dl)

Data Collection Procedure

After approval from hospital ethical committee, 140 patients fulfilling inclusion criteria was enrolled in the study from the operation theatre of Department of Obstetrics & Gynecology, Sir Ganga Ram Hospital, Lahore. Informed consent was obtained and demographics of patients (name, age, type of hysterectomy) were noted. The participants were randomly divided in two groups by using lottery method. Baseline heart rate was measured by using ECG monitor. Group M was given midazolam 2 ml (i.e 2 mg) and group C was given 2ml of physiological saline only, by a person not involved in taking observations. Then all patients followed-up till 15 minutes for assessment of heart rate (as per operational definition) and induction was done. The females then underwent hysterectomy. All this information was recorded on proforma (attached).

Data Analysis Procedure

Data was entered and analyzed using SPSS 20. Quantitative data like age, heart rate was described as Mean and standard deviation. Both groups were compared for mean heart rate by using t-test taking p-value≤ 0.05 as significant. Data was stratified for age and baseline heart rate to deal with effect modifiers. t-test was applied. p-value≤0.05 was considered as significant.

RESULTS:

In this present study total 140 cases were enrolled. The mean age of the patients was 48.11±10.30 years with minimum and maximum ages of 21 & 85 years respectively. **Table#1**

In our study the mean HR value at baseline of the patients was 88.25±11.31 per minute with minimum and maximum values of 65 and 112 per minute respectively. **Table#2**

The study results showed that the mean HR value after 15 minutes of the patients was 80.69±9.97 per minute with minimum and maximum values of 59 and 104 per minute respectively. **Table#3**

In this study the mean HR value at baseline in midazolam group was 92.26±11.013 per minute and its mean value in placebo group was 84.24±10.182 per minute. Statistically there is highly significant difference was found between the study groups and the HR value at baseline of the patients. i. e p-value=0.000. **Table#4**

In this study the mean HR value after 15 minutes in midazolam group was 80.03±9.917 per minute and its mean value in placebo group was 81.03±10.052 per minute. Statistically there is insignificant difference was found between the study groups and the HR value after 15 minutes of the patients. i. e p-value=0.437. **Table#5**

The study results showed that in below 50 years patients, the mean HR value after 15 minutes of the patients in midazolam group was 79.53±10.01 per minute and its mean value in placebo group was 83.20±9.88 per minute. Similarly in above 50 years patients,the mean HR value after 15 minutes of the patients in midazolam group was 81.19±9.84 per minute and its mean value in placebo group was 78.00±9.66 per minute. Statistically there is insignificant difference was found between the study groups and HR after 15 minutes of the

patients stratifying by age. i. e p-value=0.077 and 0.275 respectively. **Table#6**

The study results showed that inpatients with below 85 HR value at baseline, the mean HR value after 15 minutes of the patients in midazolam group was 70.32±5.83 per minute and its mean value in placebo group was 75.79±7.73 per minute. Similarly in patients with above 85 HR value at baseline,the mean HR value after 15 minutes of the patients in midazolam group was 83.65±8.62 per minute and its mean value in placebo group was 89.68±6.88 per minute. Statistically there is significant difference was found between the study groups and HR after 15 minutes of the patients stratifying by HR values at baseline. i. e p-value=0.008 and 0.002 respectively. **Table#7**

Table#1

Descriptive statistics of age (years)

Age (years)	**n**	140
	Mean	48.11
	SD	10.30
	Minimum	21
	Maximum	85

Table#2

Descriptive statistics of heart rate at baseline

HR Baseline	**n**	140
	Mean	88.25
	SD	11.31
	Minimum	65
	Maximum	112

Table#3

Descriptive statistics of heart rate after 15 minutes

HR after 15 minutes	**n**	140
	Mean	80.69
	SD	9.97
	Minimum	59
	Maximum	104

Table#4

Comparison of HR at baseline with study groups

		Study Groups	
		Midazolam	**Placebo**
HR at baseline	**n**	70	70
	Mean	92.26	84.24
	SD	11.013	10.182

t-value=4.471

p-value=0.000 (Significant)

Table#5

Comparison of HR after 15 minutes with study groups

		Study Groups	
		Midazolam	**Placebo**
HR after 15 minutes	**n**	70	70
	Mean	80.03	81.34
	SD	9.917	10.052

t-value=-0.779

p-value=0.437 (Insignificant)

Table#6

Comparison of HR at baseline with study groups stratified by age

Age (years)	Study Groups	HR after 15 (minutes)	p-value
<50	**Midazolam**	79.53±10.01	**0.077**
	Placebo	83.20±9.88	
≥50	**Midazolam**	81.19±9.84	**0.275**
	Placebo	78.00±9.66	

Table#7

Comparison of HR at baseline with study groups stratified by HR at baseline

HR at baseline	Study Groups	HR after 15 (minutes)	p-value
<85	**Midazolam**	70.32±5.83	**0.008**
	Placebo	75.79±7.73	
≥ 85	**Midazolam**	83.65±8.62	**0.002**
	Placebo	89.68±6.88	

DISCUSSION:

This present randomized control study was carried out at department of Anesthesiology, Sir Ganga Ram Hospital, Lahore to compare the mean heart rate with midazolam premedication versus placebo in females undergoing hysterectomy under general anesthesia.

Anxiety in response to impending surgery is a common emotional phenomenon, but it also leads to perioperative physiological and psychological changes. The major goal of pre-medication is to allay anxiety [62]. Midazolam, a water soluble benzodiazepine is a useful agent for pre-medication and sedation. It has a short onset time and duration of action when compared to other benzodiazepines [63].

Midazolam is used as the pre-medication in more than 90% of surgical operations in the United State of America [2]. Intravenous midazolam reduces blood pressure and peripheral vascular resistance [7].

In our study the mean HR value at baseline in midazolam group was 92.26±11.013 per minute and its mean value in placebo group was 84.24±10.182 per minute. Statistically there is highly significant difference was found between the study groups and the HR value at baseline of the patients. i. e p-value=0.000. but after 15 minutes insignificant difference of HR was found between both the study groups. i. e p-value=0.437

A study conducted by Ehtesham I et al [64] presented that the midazolam is a good anxiolytic for pre-medication and its effect on platelet aggregation profile needs to be further evaluated. Systolic and diastolic blood pressures were compared between the two groups (midazolam & Placebo), they were significantly lower in the midazolam group after pre-medication (p<0.05) whereas there was no statistically significant change in the heart rate after pre-medication in either group.

One more study by MehrdadShoroghi et al [65] described that there were no significant differences in heart rate, respiratory rate, and systolic blood pressure among the groups. However, arterial oxygen saturation was significantly reduced in those given 1 mg.kg-1 midazolam.

Another study by M L. JAAKOLA et al [66] enrolled twenty ASA I-II elective hysterectomy patients. Ten patients received dexmedetomidine 2.5 µg kg-1 i.m. 60 min before induction and saline placebo i.v. 2 min prior to induction (= DP group). Ten patients received midazolam 0.08 mg kg-1 i.m. 60 min and fentanyl 1.5 µg kg-1 i.v. (= MF group) 2 min before induction of anaesthesia with thiopentone 4 mg kg-1. Intraoperatively systolic and diastolic arterial pressure were 15% and 13% lower in DP group (P < 0.01 and P < 0.05 for drug effect), the mean heart rate was approximately 9 beats min-1 lower in DP group (n.s.). Fentanyl was required more often in MF group.

In study by Fine et al. [67] arterial oxygen saturation and heart rate were not significant changed after the administration of 0.5 mg.kg-1 oral midazolam. In another study by Masue et al. [68] Midazolam 1.5 mg.kg-1 did not cause any statistically significant decrease in blood pressure, arterial oxygen saturation and heart rate.

A recent study in 2014, found that the heart rate with midazolam was 73.60±12.341bpm (n=35) which was significantly lower as compared to placebo (79.06±10.218bpm, n=35). The reported difference was significant (P<0.05) [3].

But a recent study in 2014, found that the heart rate with midazolam was 73.60±12.341bpm (n=35) which was significantly lower as compared to placebo (79.06±10.218bpm, n=35). The reported difference was significant (P<0.05) [6].

CONCLUSION:

Our study results concluded that the there is insignificant difference was found the mean heart rate after 15 minutes with midazolam premedication versus placebo in females undergoing hysterectomy under general anesthesia while the baseline values were statistically significant.

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PROFORMA

COMPARISON OF EFFECT OF MIDAZOLAM PRE-MEDICATION VERSUS PLACEBO ON HEMODYNAMICS IN FEMALES UNDERGOING HYSTERECTOMY UNDER GENERAL ANESTHESIA

Case No: _____ Dated: _____
Registration No: _____
Name: _____ Age: _____
Group: Midazolam □ Placebo □
Follow-up:

Outcome	Baseline	After 15 minutes
Heart Rate (bpm)		