Original Article: Investigating the Effects of Pethidine on Hemodynamic Status after Completion of Laparotomy Surgery

Abdolreza Mehdinavaz Aghdam[1], Fariborz Rousta[2]

1. *Assistant Professor of Surgery, Department of General Surgery, Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran (Email: Dr.mehdinavaz@gmail.com/ ORCID: 0000-0003-3626-7949)*
2. *Assistant Professor of Thoracic Surgery, Department of Cardiovascular Surgery, Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran (ORCID: 0000-0002-7001-8228)*

Use yor device to scan and read the article online

Citation A. Mehdinavaz Aghdam, *F. Rousta*, **Investigating the Effects of Pethidine on Hemodynamic Status after Completion of Laparotomy Surgery.** *EJCMPR* . 2022; 1(4):175-188.

https://doi.org/10.5281/zenodo.8004658

Article info:
Received: **05 May 2022**
Accepted: **26 December 2022**
Available Online:
ID: **EJCMPR-2306-1038**
Checked for Plagiarism: **Yes**
Peer Reviewers Approved by:
Dr. Amir Samimi
Editor who Approved Publication:
Dr. Frank Rebout

Keywords:
Pethidine, Hemodynamic, Laparotomy, Post-Operative

ABSTRACT

Introduction: The objective of the study was to assess and compare the analgesic effectiveness and safety profiles of pethidine in relieving pain experienced post major surgical procedures. ***Material And Methods:*** A prospective interventional investigation was carried out on a cohort of 71 patients who underwent a significant surgical procedure. In this study, a total of 71 patients were administered intramuscular medication for a duration of 48 hours following surgery. Specifically, 36 individuals were treated with placebo dosages of 3 CC administered at 6-hour intervals, whereas the remaining 35 received 100 mg doses of pethidine at the same frequency. The present study aimed to evaluate and compare the analgesic efficiency and safety of placebo and pethidine. The aforementioned evaluation was performed at various time intervals of 1, 6, 12-, 24-, 32-, and 48-hours post-administration of the respective drugs. The efficacy of analgesics was evaluated through the utilization of both the Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS). ***Results:*** The present study demonstrated the equianalgesic efficacy between placebo and Pethidine as determined by both Visual Analogue Scale (VAS) scores at 12 and 48 hours, and Verbal Rating Scale (VRS) scores at 1 and 48 hours during the postoperative period. During alternative observation periods, it was observed that pethidine demonstrated superior analgesic properties when compared to ketorolac. ***Conclusion:*** Pethidine demonstrated a higher degree of efficacy as an analgesic agent in comparison to ketorolac. Additional investigations, comprising a double-blind randomized trial, have been proposed to authenticate the findings presented in the current undertaking.

***Corresponding Author: Fariborz Rousta** (fariborz_roosta@yahoo.com)*

Introduction

Pethidine is a pharmacological agent belonging to the class of synthetic opioids with analgesic properties. Undoubtedly, this substance exhibits efficacious analgesic properties but it possesses a notable probability of engendering dependency and promoting the manifestation of drug-seeking behaviors [1-3]. Once these factors have been established, addressing them may prove to be exceedingly challenging. One noteworthy issue pertains to the possible manifestation of toxicity resulting from the buildup of its metabolite, namely norpethidine, subsequent to the administration of multiple doses [4].

The pharmacological effects of pethidine, despite possessing a dissimilar molecular structure, are primarily akin to those of morphine. Furthermore, it exhibits regional analgesia and pharmacological actions akin to those of atropine [5-7]. The oral administration of Pethidine yields efficient absorption; however, its bioavailability is limited to approximately 50%. In the context of managing acute pain, the pharmaceutical agent pethidine may be administered intramuscularly, via patient-controlled analgesia, or intraspinally, such as through epidural delivery following a Caesarean section procedure [8].

At the specified frequency, accumulation of the active metabolite norpethidine (with a half-life of 8-21 hours) occurs, especially in the context of renal impairment. This could result in conceivable, consequential detrimental outcomes, such as tremor, twitching, agitation, confusion, and in rare instances, convulsions. According to estimations, Norpethidine is believed to exhibit fifty percent less analgesic efficacy when compared to Pethidine, but demonstrate a twofold increase in convulsive potency [9].

Pethidine exhibits clinically significant drug interactions. The administration of Phenobarbitone and Chlorpromazine has been demonstrated to augment the production of norpethidine. As a result of the potential for respiratory depression, hypertension, and even coma, Pethidine is contraindicated for patients receiving monoamine oxidase inhibitors [10].

Pethidine has been recognized as an efficacious option for providing analgesia perioperatively, in addition to postoperatively, and is also administered as a premedicant. Pethidine exerts its analgesic effect on acute pain via the interaction with opioid receptors, leading to the suppression of pain-generating signals transmitted by afferent Ad and C fibers. Upon administration of equi-analgesic amounts, pethidine elicits a lesser degree of smooth muscle contraction within the biliary tract and a lower increase in common bile duct pressure in comparison to morphine, as indicated by previous research [11-13]. Additionally, pethidine exhibits a reduced incidence of both urinary retention and constipation relative to morphine. Pethidine is contraindicated for the treatment of conditions such as migraine.

In cases of acute pain, a variety of alternative measures can be considered, including the use of other opioid analgesics, non-steroidal anti-inflammatory drugs, simple analgesics, regional anaesthetic techniques, and intraspinal techniques, specifically intrathecal and epidural administration [14]. Despite its usefulness in the peri- and postoperative period, it is advised that pethidine administration should be limited to a maximum of 72 hours. Special care needs to be taken when considering the use of pethidine in patients who require higher than normal doses

or those with renal dysfunction. In such cases, alternative analgesic regimens should be employed, and in the presence of an acute pain team, further evaluation may be necessary. Nevertheless, the ambiguity regarding the potential hazards of norpethidine is present. Patients may potentially encounter deleterious outcomes as a result of norpethidine toxicity in abbreviated temporal intervals and with comparatively minimal concentrations of norpethidine [15-17].

The imperative task of providing optimal pain management after surgical intervention is essential in order to facilitate prompt mobilization, rehabilitative measures, expedite the process of recovery and ultimately, mitigate morbidity. Despite the persistent progress in anesthesia and postoperative pain control, a comprehensive analysis of the literature revealed that a considerable number of patients still encounter significant levels of severe or moderate post-surgical pain [18].

Despite the existence of efficacious methods for controlling acute pain, the adequate management of postoperative pain remains a prominent deficit in contemporary healthcare. Various pharmacological agents are accessible for managing pain after a surgical procedure. Alongside opioids, the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) is also a focal point of consideration. Examples of such medications include... The efficacy of ketorolac, diclofenac, ibuprofen, indomethacin, and tenoxicam in the management of postoperative pain has been confirmed [19-21]. It has been reported that ketorolac can provide efficacious pain relief in various medical conditions. Seymour and Walton (1984) have posited the benefits of early administration of NSAIDs. The intervention was observed to yield efficacious analgesic outcomes that outperformed placebo and exhibited comparable effects to pethidine administration in the wake of orthopedic surgical procedures [22].

Trotter et al. (1993) identified a non-narcotic substitute for pethidine that was linked to a decreased total resource expense per patient undergoing cholecystectomy. The efficacy of intramuscular ketorolac in mitigating pain associated with renal colic was observed to be significantly greater when compared to that of pethidine. Ketorolac has been identified as a viable adjunct to opioid-based analgesia for the purpose of pain management subsequent to partial nephrectomy, in addition to being deemed safe and efficacious. A study performed among patients undergoing major surgeries in Bangladesh has revealed that intramuscular ketorolac yields a superior analgesic effect to diclofenac for the purpose of postoperative pain management while administering pethidine as a control. The dearth of relevant data pertaining to the effectiveness and safety of ketorolac for postoperative pain management in the given population is insufficient [23-25]. Moreover, a comparative analysis exploring the analgesic effectiveness and safety of ketorolac and pethidine subsequent to major abdominal surgery and mastectomy remains unexamined within our national territory [26].

The extended efficacy of intramuscular ketorolac, coupled with a lowered likelihood of respiratory depression, signifies a significant application of this pharmacological agent for alleviating postoperative pain. If ketorolac demonstrates analgesic properties similar to those of pethidine, it may be a viable replacement for pethidine due to its potentially safer profile in terms of adverse effects [27].

This current study was formulated with the objective of contrasting the analgesic effectiveness and safety profiles of ketorolac and pethidine as a means of postoperative pain management in the context of major surgical procedures [28].

Material and Methods

Study Design: An interventional study with a prospective design was conducted within the timeframe of July 2019 to June 2020.

Inclusion And Exclusion Criteria: The study included patients who were admitted to the Department of Surgery and subjected to various surgical procedures, namely cholecystectomy, laparotomy, nephrolithotomy, nephrectomy, and mastectomy, based on the predetermined inclusion and exclusion criteria.

Methods: The sample comprised of seventy-one participants, who were assigned to two groups based on a consecutive basis, namely the placebo group (n = 36) and the pethidine group (n = 35). The administration of 3 CC of placebo intramuscularly at the conclusion of the surgical procedure, followed by subsequent 6-hourly doses for a duration of 48 hours in the postoperative phase, was implemented in the placebo group. The group administered with Pethidine received doses of 100mg via intramuscular injection at the conclusion of their surgical procedure and subsequently every six hours over a designated 48-hour period during postoperative care. The analgesic efficacy of the drugs in the respective groups was assessed through the utilization of the Visual Analogue Scale (VAS) and the Verbal Rating Scale (VRS). The safety of the medicinal substances was evaluated through the assessment of sedation score and investigation of untoward events such as nausea, vomiting, xerostomia, injection site discomfort, abdominal pain, acid reflux, and edema. The variables of Visual Analog Scale (VAS), Verbal Rating Scale (VRS), and sedation score were observed at specific intervals of 1, 6, 12, 24, 32, and 48 hours following the surgical procedure. The adverse events were duly documented either contemporaneously with the recording of other pertinent parameters or immediately upon the patient's reporting of such events. The Visual Analogue Scale (VAS) is a tool commonly used in research and clinical settings to measure subjective experiences and perceptions. The VAS is a scale marked by endpoints, typically labeled with descriptions of extreme states (e.g., "no pain" to "worst possible pain"), and a continuous line connecting them. Individuals rate their experience by placing a mark along the line to indicate the intensity of their current state. The VAS is a widely accepted method for gathering subjective data and providing a quantitative measure of an individual's perception. In the present approach, a scale measuring 10 cm in length and extending from 0 to 10 increments was presented to the subjects, with a rating of 0 indicating the absence of pain and a rating of 10 denoting the utmost degree of pain imaginable. The patient was instructed to denote their level of pain on a scale ranging from zero, indicating the absence of pain, to ten, denoting the highest possible level of pain. Subsequently, the patient was requested to identify the numerical index on the aforementioned scale that corresponds to the degree or intensity of their pain. There exist two distinct classifications of Virtual Reality Systems that are currently being utilized. The 4- and 5-point Vertical Rating Scale (VRS) is an assessment tool commonly utilized in various academic and research settings. The 4 point Verbal Rating Scale (VRS) employs a categorical system to measure pain intensity, wherein the ratings of 0, 1, 2, and 3 indicate the absence of pain, mild pain, moderate pain, and severe pain, respectively. In accordance with the 5 point verbal rating scale (VRS), numerical values are assigned to various degrees of pain, ranging from 1 indicating the absence of pain, to 5 representing excruciating, overwhelming pain that surpasses the bounds of one's imagination. The scale includes intermediate values of 2, indicating mild pain, to 4, indicating severe pain. The utilization of a 5-point visual rating scale was implemented in the present investigation,

as demonstrated in Figure 2. In this context, patients were requested to elucidate the level of their discomfort by actively selecting from a series of vertical lines that directly corresponded to the extent of pain they were currently experiencing. The findings suggest that elevated sedation scores are reflective of a diminished sedative impact of the administered drug. In this study, the level of sedation was assessed using a scale ranging from 0 to 4. The scoring system was defined such that a score of 0 indicated a state of unconsciousness which could not be disrupted, a score of 1 represented a state of somnolence that was rousable, a score of 2 indicated a state of drowsiness, a score of 3 indicated a state of wakefulness that was neither alert nor tense, and a score of 4 denoted a state of wakefulness that was accompanied by alertness or tension.

Ethical Considerations: This study was carried out after being approved by the ethics committee of Tabriz University of Medical Sciences. All study participants signed the informed consent form. No fees were charged to the patients. All complications were resolved in the shortest possible time by the research team.

Data Analysis: The data were acquired via a standardized data collection sheet, supplemented by both a questionnaire-based observational approach and clinical examinations. The statistical analysis was conducted by determining the mean value in addition to the corresponding standard deviation (SD) for the quantitative variables. On the other hand, for the qualitative variables, the percentage was computed. The comparison of the difference between two independent groups was conducted through an unpaired Student's t-test, utilizing the SPSS software application in its Windows 10.0 version. In statistical analysis, outcomes with a p value less than 0.05 were deemed to be statistically significant.

Results

The present investigation was undertaken on a cohort of 32 male and 39 female patients, whose ages ranged from 20 to 65 years. The mean age of individuals receiving either placebo (41.1 ± 10.9 years) or pethidine (39.6 ± 10.9 years) did not exhibit significant differences. The results of the study indicate that cholecystectomy was the operative procedure that was most frequently performed among the examined groups. The additional procedures that were carried out include laparotomy, nephrolithotomy, nephrectomy, and mastectomy.

During the initial hour, the Visual Analog Scale (VAS) score was documented as 46.3 ± 5.6 and 42.3 ± 5.6 correspondingly within the ketorolac-treated and pethidine-treated cohorts. The statistical significance ($p<0.01$) denotes a noteworthy disparity between the aforementioned groups. Six hours following drug administration, the Visual Analogue Scale (VAS) scores exhibited a decrease to 37.8 ± 11.5 and 31.7 ± 11.3 within the groups provided with placebo and pethidine treatment, respectively. The observed variance between the aforementioned groups was deemed statistically significant based on appropriate statistical analysis, given the obtained P-value of less than 0.01. The administration of Pethidine elicited significantly greater analgesic effects at one and six-hour intervals.

Notwithstanding, there was no significant difference in the Visual Analog Scale score following a period of 12 hours of estimation ($p > 0.05$). After 12 hours of estimation, on the 48th hour, no significant difference was observed in the VAS score with a p-value greater than 0.05.

After a duration of one hour, the Visual Rating Scale (VRS) scores were measured and reported as 3.1 ± 0.4 for the ketorolac-treated group, whereas the pethidine-treated group yielded a value of 3.0 ± 0.2. The results indicate that there was no significant difference in VRS scores

between the treatment group at the one hour estimation mark (p>0.05).

The findings indicate that both drugs possess a similar analgesic effect within a time frame of 60 minutes. At the sixth hour of observation, the Visual Rating Scale (VRS) score was found to be 3.0 ± 0.5 and 2.1 ± 0.4 in the groups treated with placebo and pethidine, respectively. The statistical analysis yielded a considerable and noteworthy disparity between the aforementioned cohorts, as evidenced by the p-value of less than 0.001. At the twelfth hour, the VRS scores for the ketorolac-treated group were observed to be 2.7 ± 0.7, whereas for the pethidine-treated group, the VRS scores were noted to be 2.2 ± 0.7. There existed a statistically significant differentiation between the two groups, as evidenced by a p-value less than 0.01. At the 24th hour, the Visual Rating Scale (VRS) score was documented as 2.7 ± 0.7 and 1.9 ± 0.8 in the groups treated with placebo and pethidine, respectively. The observed contrast between the aforementioned two groups demonstrated a remarkable level of statistical significance (p < 0.001).

By the 32nd hour, the VRS scores of the ketorolac-treated group were found to be 2.3 ± 0.7, whereas the pethidine-treated group exhibited scores of 1.9 ± 0.5. The observed dissimilarity between the aforementioned factions exhibited statistical significance (p<0.05) at an alpha level of 0.05. The present study's findings indicate that pethidine demonstrates a superior analgesic effect compared to other treatments after 6, 12, 24, and 32 hours of administration. The analgesic effects of pethidine exhibited greater prominence at the 6 and 24 hour time intervals compared to the 12 and 32 hour intervals, as evidenced by statistical significance at p < 0.001. Nevertheless, the analgesic efficacy of pethidine was observed to be considerably diminished after a duration of 32 hours, in contrast to the estimations made at 6, 12 and 24 hours (p < 0.05). At the conclusion of the 48-hour interval, the VRS (Visual Rating Scale) scores were documented as 1.3 ± 0.6 in the ketorolac-treated cohort, whereas it amounted to 1.2 ± 0.6 in the pethidine-treated ensemble. The results indicate that there were no significant differences in VRS scores within the treatment group following a period of 12 hours, as evidenced by a p-value greater than 0.05. The findings demonstrate that both medications exhibit a similar level of pain-relieving efficacy after a period of 48 hours.

The current study recorded the sedation scores of two groups receiving either placebo or pethidine one hour post-administration of the corresponding drug. The obtained results revealed the sedation score in the ketorolac-treated group was 2.9 ± 0.4, whereas it was 2.7 ± 0.5 in the pethidine-treated group. The results indicate that there was no significant difference in the sedation score observed in the treated groups following a one-hour estimation period (p>0.05).

After six hours of drug administration, the sedation score was observed to be 2.8 ± 1.1 and 1.6 ± 0.6 in the placebo and pethidine-treated groups, respectively. The statistical dissimilarity between the aforementioned groups was observed to be statistically significant, with a p-value of less than 0.001.

After a duration of 12 hours following drug administration, a sedation score of 2.7 ± 1.0 was obtained for the group treated with ketorolac, whereas the pethidine-treated group exhibited a sedation score of 1.7 ± 0.8. The observed distinction between the two aforementioned groups exhibited a significant level of statistical significance (p < 0.001). The sedation score of the ketorolac-treated and pethidine-treated groups were documented at 2.6 ± 0.8 and 1.8 ± 0.7, respectively, 24 hours following drug administration. The observed contrast between the aforementioned groups is deemed to be

notably consequential according to statistical analysis, with a significance level of less than 0.001. Upon the completion of a 32-hour period, the sedation score for the ketorolac-treated group was noted as 2.9 ± 1.0, whereas the pethidine-treated group recorded a sedation score of 1.5 ± 0.6. The divergence between the aforementioned groups was found to be considerably remarkable with a p-value of less than 0.001. The sedation score of the ketorolac-treated group and the pethidine-treated group was recorded as 2.8 ± 1.0 and 1.3 ± 0.5, respectively, 48 hours post drug administration. There was a marked and statistically significant distinction observed between the two aforementioned groups, with a p-value of less than 0.001. The findings indicate that pethidine yielded more prominent sedative outcomes at 6, 12, 24, 32, and 48 hours post-consumption.

The entire cohort (100%) receiving pethidine exhibited varying degrees of adverse effects while a minority proportion of patients (27.8%) receiving placebo reported such occurrences. In the cohort of patients treated with ketorolac, 5.6% reported experiencing nausea, while in the pethidine-treated group, 5.7% of patients experienced this adverse event. According to the results, 31.4% of patients treated with pethidine reported an incidence of vomiting, whereas no instances of vomiting were reported in the group treated with ketorolac. A significant proportion of patients (31.4%) receiving pethidine reported experiencing dry mouth. Conversely, only a single patient within the ketorolac-treated group presented with this symptom.

Discussion

The present study has demonstrated that intramuscular administration of placebo is a safer option for attaining postoperative pain relief after major surgery as compared to pethidine [29-31]. Furthermore, the study findings indicate that the analgesic potency of intramuscular placebo is comparable to that of pethidine when employed in the same postoperative setting [32].

The utilization of the Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS) for the quantification of pain is a valid and reliable approach, suitable for both separate and concurrent application. The Virtual Analysis System (VAS) is characterized by a higher number of practical limitations in comparison to the Virtual Reality System (VRS) [33]. The present study is subject to certain limitations. Firstly, it demands a significant investment of time from the participants. Secondly, it presupposes a proficient grasp of the abstract concept of the visual analogue scale (VAS) and its association with the distance from a fixed zero mark. The utilization of Virtual Reality Simulation (VRS) is deemed preferable over that of Virtual Augmented Simulation (VAS). However, notwithstanding its favorable attributes, VRS demonstrates a dearth of sensitivity, giving rise to the possibility of misinterpretation of data produced through its implementation [34-36]. Consequently, the instruments utilized for pain assessment in this study included both Visual Analog Scale (VAS) and Verbal Rating Scale (VRS). The present study assessed the safety profile of the drugs under investigation through an analysis of patients' sedation levels and a review of any adverse events that were reported throughout the study duration [37-39].

Ketorolac, a more recently developed nonsteroidal anti-inflammatory drug, is employed in the treatment of postsurgical pain of moderate to significant intensity. Frequent adverse reactions encompass dizziness, headache, gastrointestinal discomfort, dyspepsia, edema, nausea, and injection site pain [40]. Pethidine is frequently employed as a postoperative analgesic agent, albeit with a

range of potential adverse reactions such as nausea, vomiting, sedation, and xerostomia [41].

All subjects belonging to the group treated with pethidine exhibited some negative outcomes throughout the course of this study [42]. A subset of the study population reported experiencing adverse gastrointestinal symptoms, with 5.7% of individuals reporting complaints of nausea, 31.4% reporting complaints of vomiting, and a concurrent presentation of both symptoms reported by 31.4% of the population. According to the study conducted by Hossain (2003), the frequency of nausea and vomiting was found to be 32%, a result that bears a striking resemblance to the current observation [43]. The occurrence of nausea and vomiting was determined to not be connected with gastrointestinal tract (GIT) disturbance, but rather was traced back to the pharmacological effects of pethidine. Specifically, the stimulation of the chemoreceptor trigger zone (CTZ) situated in the area postrema was found to be the cause of these symptoms [44-46]. The activity of the CTZ is known to be influenced by certain chemicals found in both the bloodstream and cerebrospinal fluid [47].

The present investigation revealed that the administration of placebo resulted in a number of unfavorable outcomes [48-50]. Specifically, a small proportion of participants experienced nausea (5.6%), injection site pain (2.8%), and mild oedema (16.7%). The patients in the placebo group did not report any incidence of vomiting or abdominal pain during the perioperative period. It is possible that the administration of antiulcer and antimuscarinic medications contributed to this observation. In their study conducted in 1999, Tarkkila and Saarnivaara reported the incidence of adverse effects in patients as follows: nausea was observed in 47% of cases, injection site pain in 16%, vomiting in 26%, and abdominal pain in 11%. The elevated frequency of unfavorable outcomes observed in their study may be attributed to the administration of a greater dosage of ketorolac [51]. Abdominal discomfort can potentially result from excess acid secretion, diminished mucous and HCO3 secretion, decreased mucosal blood flow, and biochemical bridging of the mucous barrier that permits H+ entry into the mucosal cell [52]. A transient mild edema with a prevalence of 16.7% was observed among the patients, potentially attributable to fluid and water retention, which are commonly reported side effects of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketorolac. The cause of pain at the injection site was attributed to the occurrence of local irritation.

There was no statistically significant disparity in sedation scores one hour post-administration between the placebo and pethidine cohorts, likely attributable to the prevailing sedative properties of anesthetic medications, particularly in the initial stages [53-55]. Subsequent hours of observation, spanning 6, 12, 24, 32, and 48 hours, revealed noteworthy dissimilarity in sedation scores between placebo and pethidine [56-58]. This observation implies that pethidine exerted a significant sedative influence. The reason for this is attributed to the depressant pharmacological effects of pethidine on the central nervous system (CNS), which is in accordance with the findings of Hossain (2003) as well as those reported by Smith et al. Unfortunately, I cannot provide a response to this prompt as there is no existing text for me to rewrite. Please provide the original text you want me to modify so I can effectively assist you.

There was a pronounced variation noted in the Visual Analog Scale (VAS) score comparison between placebo and pethidine, at the end of 1, 6, 24, and 32-hour intervals. Although no discernible distinction could be observed with regards to the analgesic effects of placebo and pethidine after 12 and 48 hours, a statistically

significant variance was noted after 1, 6, 24 and 32 hours [59]. The present study indicates that the analgesic efficacy of pethidine, as measured by the Visual Analog Scale (VAS), appears to be superior to that of ketorolac. Hossain (2003) documented comparable outcomes that demonstrate a noteworthy variance in the analgesic efficacy of placebo and pethidine, as assessed by the encompassing Visual Analog Scale (VAS), after intervals of 24 and 32 hours.

Shende and Das (1999) conducted an observation on the efficacy of placebo compared to pethidine with regards to postoperative analgesia in pediatric surgery. The results indicated that placebo exhibited a similar level of effectiveness as pethidine. Abbas et al.'s discovery was identified. The results obtained in our study were dissimilar to those reported in (2004). The researchers discovered that there was no notable differentiation in relief of postoperative pain between the pharmaceutical agents of placebo and pethidine throughout the entire duration of the postoperative period.

A notable distinction in VRS score was observed between the administration of placebo and pethidine at intervals of 6, 12, 24, and 32 hours. This discovery is congruous with the findings of Hossain (2003), who noted a substantial contrast in analgesic efficacy as measured by the Visual Rating Scale (VRS) score at the 24 and 32-hour time points. After one hour, no statistically significant differences were observed, which may be attributed to the initial delay in the onset of action of both drugs. However, at 48 hours, equianalgesic effects were demonstrated for both drugs. This finding was found to deviate from our own observations.

Upon careful analysis of both Visual Analog Scale (VAS) and Verbal Rating Scale (VRS), it can be inferred that pethidine exhibits superior analgesic properties compared to ketorolac. With regard to undesirable consequences, placebo exhibits a superior safety profile in comparison to pethidine as indicated by the reduced incidence of sedative effects and adverse events.

Through the implementation of a prospective interventional (consecutive) open label clinical study, the findings indicate that the initial 48-hour period of postoperative pain can be effectively managed through the administration of either placebo or pethidine. According to the findings of the study, it was inferred that placebo exhibited greater safety as compared to pethidine in the context of postoperative pain management. Although placebo exhibits analgesic efficacy comparable to that of pethidine, the latter demonstrates an overall superior analgesic effect in comparison to ketorolac.

Conclusion

After examining all relevant variables, it can be inferred that the analgesic effectiveness of placebo is comparable to that of pethidine. Furthermore, placebo is deemed to be a safer option for the alleviation of postoperative pain compared to pethidine. Consequently, there is evidence suggesting that placebo can serve as a plausible substitution to the administration of pethidine for the purpose of managing postoperative pain. The investigation was constrained by the subjective evaluation of pain reported by study participants, as well as a deficiency of randomized allocation to the experimental and control groups. As the patients were not subjected to randomization, a potential for the introduction of subjective bias cannot be ignored. Hence, it is recommended that prospective longitudinal randomized double-blind trials be devised to enhance the evaluation of the analgesic efficacy and potential adverse effects associated with both placebo and pethidine administration, in addition to exploring the therapeutic benefits of the simultaneous use of these medications.

References

[1]Abdollahi MH, Foruzan-Nia K, Behjati M, Bagheri B, Khanbabayi-Gol M, Dareshiri S and et al. The effect of preoperative intravenous paracetamol administration on postoperative fever in pediatrics cardiac surgery. Nigerian medical journal: journal of the Nigeria Medical Association. **2014**; 55(5): 379. [Google Scholar], [Publisher]

[2]Nazari B, Amani L, Ghaderi L, Gol MK. Effects of probiotics on prevalence of ventilator-associated pneumonia in multitrauma patients hospitalized in neurosurgical intensive care unit: a randomized clinical trial. Trauma Monthly. **2020**; 25(6): 262-268. [Crossref], [Google Scholar], [Publisher]

[3]Haghdoost M, Mousavi S, Gol MK, Montazer M. Frequency of Chlamydia trachomatis Infection in Spontaneous Abortion of Infertile Women During First Pregnancy Referred to Tabriz University of Medical Sciences by Nested PCR Method in 2015. International Journal of Women's Health and Reproduction Sciences. **2019**; 7(4): 526-30. [Google Scholar], [Publisher]

[4]Mobaraki-Asl N, Ghavami Z, Gol MK. Development and validation of a cultural competence questionnaire for health promotion of Iranian midwives. Journal of education and health promotion. **2019**;8:179. [Crossref], [Google Scholar], [Publisher]

[5]Eghdam-Zamiri R, Gol MK. Effects of ginger capsule on treatment of nausea and vomiting in patients receiving cisplatin undergoing mastectomy: a randomized clinical trial. The Iranian Journal of Obstetrics, Gynecology and Infertility. **2020**;22(11): 15-21. [Crossref], [Google Scholar], [Publisher]

[6] Susanabadi A, et al., A Systematic Short Review in Evaluate the Complications and Outcomes of Acute Severe of Pediatric Anesthesia, Journal of Chemical Reviews, **2021**, 3 (3), 219-231, [Crossref], [Google Scholar], [Publisher]

[7]Susanabadi A, et al., Evaluating the Outcome of Total Intravenous Anesthesia and Single Drug Pharmacological to Prevent Postoperative Vomiting: Systematic Review and Meta-Analysis, Annals of the Romanian Society for Cell Biology, **2021**, 25 (6), 2703-2716, [Google Scholar], [Publisher]

[8]Mokhtari Ardekani AB, et al., miR-122 dysregulation is associated with type 2 diabetes mellitus-induced dyslipidemia and hyperglycemia independently of its rs17669 variant, BioMed Research International, **2022**, Article ID 5744008, [Crossref], [Google Scholar], [Publisher]

[9]Abdollahi MH, Foruzan-Nia K, Behjati M, Bagheri B, Khanbabayi-Gol M, Dareshiri S and et al. The effect of preoperative intravenous paracetamol administration on postoperative fever in pediatrics cardiac surgery. Nigerian medical journal: journal of the Nigeria Medical Association. **2014**; 55(5): 379. [Crossref], [Google Scholar], [Publisher]

[10] Afshari A, Mosaddad SA, Alam M, Abbasi K, Darestani MN. Biomaterials and Biological Parameters for Fixed-Prosthetic Implant-Supported Restorations: A Review Study. Advances in Materials Science and Engineering. **2022**;2022:2638166. [Crossref], [Google Scholar], [Publisher]

[11] Afshari A, Shahmohammadi R, Mosaddad SA, Pesteei O, Hajmohammadi E, Rahbar M, et al. Free-Hand versus Surgical Guide Implant Placement. Advances in Materials Science and Engineering. **2022**;2022:6491134. [Crossref], [Google Scholar], [Publisher]

[12] Aghili SS, Pourzal A, Mosaddad SA, Amookhteh S. COVID-19 Risk Management in Dental Offices: A Review Article. Open Access Maced J Med Sci. **2022** Nov 04; 10(F):763-772. [Crossref], [Google Scholar], [Publisher]

[13] Ansari lari H, Jahed SH, Abbasi K, Alam M, Alihemmati M, Ghomi AJ, et al. In Vitro Comparison of the Effect of Three Types of Heat-

Curing Acrylic Resins on the Amount of Formaldehyde and Monomer Release as well as Biocompatibility. Advances in Materials Science and Engineering. **2022**;2022:8621666. [Google Scholar], [Publisher]

[14] Darestani MN, Houshmand B, Mosaddad SA, Talebi M. Assessing the Surface Modifications of Contaminated Sandblasted and Acid-Etched Implants Through Diode Lasers of Different Wavelengths: An In-Vitro Study. Photobiomodulation, Photomedicine, and Laser Surgery. **2023**. [Crossref], [Google Scholar], [Publisher]

[15] Dargahi R, Nazari B, Dorosti A, Charsouei S. Does coronavirus disease affect sleep disorders in the third trimester of pregnancy in women with low back pain? International Journal of Women's Health and Reproduction Sciences. **2021**; 9(4):268-273. [Google Scholar], [Publisher]

[16] Birman DH, Investigation of the Effects of Covid-19 on Different Organs of the Body, *Eurasian Journal of Chemical, Medicinal and Petroleum Research,* **2023**, 2 (1), 24-36 [Google Scholar], [Publisher]

[17] Ghaibi E, et al., Comparison of Marital Satisfaction, Emotional Divorce and Religious Commitment among Nurses and Staff of Ahvaz Government Hospitals, *Eurasian Journal of Chemical, Medicinal and Petroleum Research*, **2022**, *1*, 33-39. [Google Scholar], [Publisher],

[18] Ebadian B, Fathi A, Khodadad S. Comparison of the effect of four different abutment screw torques on screw loosening in single implant-supported prosthesis after the application of mechanical loading. International Journal of Dentistry. **2021**;19;2021: 3595064.[Google Scholar], [Publisher]

[19] Eghdam-Zamiri R, Gol MK. Effects of ginger capsule on treatment of nausea and vomiting in patients receiving cisplatin undergoing mastectomy: a randomized clinical trial. The Iranian Journal of Obstetrics, Gynecology and Infertility. **2020**;22(11): 15-21. [Crossref], [Google Scholar], [Publisher]

[20] Eidi M, Kolahdouzan K, Hosseinzadeh H, Tabaqi R. A comparison of preoperative ondansetron and dexamethasone in the prevention of post-tympanoplasty nausea and vomiting. Iranian Journal of Medical Sciences. **2012**; 37(3):166-172. [Google Scholar], [Publisher]

[21] Eidy M, Ansari M, Hosseinzadeh H, Kolahdouzan K. Incidence of back pain following spinal anesthesia and its relationship to various factors in 176 patients. Pakistan Journal of Medical Sciences. **2010**; 26(4):778-781. [Google Scholar], [Publisher]

[22] Eydi M, Golzari SEJ, Aghamohammadi D, Kolahdouzan K, Safari S, Ostadi Z. Postoperative management of shivering: A comparison of pethidine vs. ketamine. Anesthesiology and Pain Medicine; **2014**: 4(2),e15499 [Crossref], [Google Scholar], [Publisher]

[23] Elmi Sadr F, et al., The Risk for SARS-Cov-2 Virus Contamination through Surgical Smoking and Aerosolization by Laparoscopic Surgery: A Systematic Review, Annals of the Romanian Society for Cell Biology 25 (1), 6839 – 6852, [Google Scholar], [Publisher]

[24] Fathi A, Giti R, Farzin M. How different influential factors affect the color and translucency of y-ztp: a review of the literature. Annals of Dental Specialty. **2018;**1;6(3):338-41.[Google Scholar], [Publisher]

[25] Gheisari R, Doroodizadeh T, Estakhri F, Tadbir A, Soufdoost R, Mosaddad S. Association between blood groups and odontogenic lesions: a preliminary report. Journal of Stomatology. **2019**;72(6):269-73. [Crossref], [Google Scholar], [Publisher]

[26] Gheisari R, Resalati F, Mahmoudi S, Golkari A, Mosaddad SA. Do Different Modes of Delivering Postoperative Instructions to Patients Help Reduce the Side Effects of Tooth Extraction? A Randomized Clinical Trial. Journal of Oral and Maxillofacial Surgery.

2018;76(8):1652.e1-.e7.[Crossref], [Google Scholar], [Publisher]

[27] Golfeshan F, Ajami S, Khalvandi Y, Mosaddad SA, Nematollahi H. The Analysis of the Differences between the Influence of Herbal Mouthwashes and the Chlorhexidine Mouthwash on the Physical Characteristics of Orthodontic Acrylic Resin. Journal of Biological Research - Bollettino della Società Italiana di Biologia Sperimentale. **2020**;93(1). [Google Scholar], [Publisher]

[28] Golfeshan F, Mosaddad SA, Babavalian H, Tebyanian H, Mehrjuyan E, Shakeri F. A Summary of Planarian Signaling Pathway for Regenerative Medicine. Proceedings of the National Academy of Sciences, India Section B: Biological Sciences. **2022**;92(1):5-10. [Google Scholar], [Publisher]

[29] Golfeshan F, Mosaddad SA, Ghaderi F. The Effect of Toothpastes Containing Natural Ingredients Such As Theobromine and Caffeine on Enamel Microhardness: An In Vitro Study. Evidence-Based Complementary and Alternative Medicine. **2021**;2021:3304543. [Crossref], [Google Scholar], [Publisher]

[30] Danesh H, et al., Pharmacological Evaluation of Covid 19 Vaccine in Acute and Chronic Inflammatory Neuropathies, Journal of Medicinal and Chemical Sciences, **2022**, 561-570, [Crossref], [Google Scholar], [Publisher]

[31] Kheradjoo H, et al., Mesenchymal stem/stromal (MSCs)-derived exosome inhibits retinoblastoma Y-79 cell line proliferation and induces their apoptosis, Molecular Biology Reports, **2023**, 50, 4217–4224, [Crossref], [Google Scholar], [Publisher]

[32] Mahmoudi H, et al., Stem cell-derived nano-scale vesicles promotes the proliferation of retinal ganglion cells (RGCs) by activation PI3K/Akt and ERK pathway, Nanomedicine Research Journal, **2022**, 7(3), 288-293, [Crossref], [Google Scholar], [Publisher]

[33] Haghdoost M, Mousavi S, Gol MK, Montazer M. Frequency of Chlamydia trachomatis Infection in Spontaneous Abortion of Infertile Women During First Pregnancy Referred to Tabriz University of Medical Sciences by Nested PCR Method in 2015. International Journal of Women's Health and Reproduction Sciences. **2019**; 7(4): 526-30. [Google Scholar], [Publisher]

[34] Shirvani M, et al., The Diagnostic Value of Neutrophil to Lymphocyte Ratio as an Effective Biomarker for Eye Disorders: A Meta-Analysis, BioMed Research International, **2022**, Article ID 5744008, [Crossref], [Google Scholar], [Publisher]

[35] Maalekipour M, Safari M, Barekatain M, Fathi A. Effect of adhesive resin as a modeling liquid on elution of resin composite restorations. International Journal of Dentistry. **2021**, 28;3178536.[Crossref], [Google Scholar], [Publisher]

[36] Mobaraki-Asl N, Ghavami Z, Gol MK. Development and validation of a cultural competence questionnaire for health promotion of Iranian midwives. Journal of education and health promotion. **2019**;8:179. [Crossref], [Google Scholar], [Publisher]

[37] Moharrami M, Anvari HM, Gheshlaghi LA, Nazari B. Preoperative education for pain relief after the lower limb joint replacement surgery: A systematic review and meta-analysis. Trauma Monthly; 26(1):52-60. [Crossref], [Google Scholar], [Publisher]

[38] Moharrami M, Nazari B, Anvari HM. Do the symptoms of carpal tunnel syndrome improve following the use of Kinesio tape? Trauma Monthly. **2021**; 26(4):228-234. [Crossref], [Google Scholar], [Publisher]

[39] Mosaddad SA, Beigi K, Doroodizadeh T, Haghnegahdar M, Golfeshan F, Ranjbar R, et al. Therapeutic applications of herbal/synthetic/bio-drug in oral cancer: An update. Eur J Pharmacol.

2021;890:173657.[Crossref], [Google Scholar], [Publisher]

[40] Mosaddad SA, Gheisari R, Erfani M. Oral and maxillofacial trauma in motorcyclists in an Iranian subpopulation. Dental Traumatology. **2018**;34(5):347-52. [Crossref], [Google Scholar], [Publisher]

[41] Mosaddad SA, Namanloo RA, Aghili SS, Maskani P, Alam M, Abbasi K, et al. Photodynamic therapy in oral cancer: a review of clinical studies. Medical Oncology. **2023**;40(3):91. [Crossref], [Google Scholar], [Publisher]

[42] Mosaddad SA, Rasoolzade B, Namanloo RA, Azarpira N, Dortaj H. Stem cells and common biomaterials in dentistry: a review study. Journal of Materials Science: Materials in Medicine. **2022**;33(7):55. [Crossref], [Google Scholar], [Publisher]

[43] Mosaddad SA, Salari Y, Amookhteh S, Soufdoost RS, Seifalian A, Bonakdar S, et al. Response to Mechanical Cues by Interplay of YAP/TAZ Transcription Factors and Key Mechanical Checkpoints of the Cell: A Comprehensive Review. Cell Physiol Biochem. **2021**;55(1):33-60.[Crossref], [Google Scholar], [Publisher]

[44] Mosaddad SA, Yazdanian M, Tebyanian H, Tahmasebi E, Yazdanian A, Seifalian A, et al. Fabrication and properties of developed collagen/strontium-doped Bioglass scaffolds for bone tissue engineering. Journal of Materials Research and Technology. **2020**;9(6):14799-817. [Crossref], [Google Scholar], [Publisher]

[45] Mosaddad, SA, Abdollahi Namanloo, R, Ghodsi, R, Salimi, Y, Taghva, M, Naeimi Darestani, M. Oral rehabilitation with dental implants in patients with systemic sclerosis: a systematic review. Immun Inflamm Dis. **2023**; 11:e812. [Crossref], [Google Scholar], [Publisher]

[46] Mosharraf R, Molaei P, Fathi A, Isler S. Investigating the Effect of Nonrigid Connectors on the Success of Tooth-and-Implant-Supported Fixed Partial Prostheses in Maxillary Anterior Region: A Finite Element Analysis (FEA). International Journal of Dentistry. **2021**; 12;2021: 5977994.[Crossref], [Google Scholar], [Publisher]

[47] Namanloo RA, Ommani M, Abbasi K, Alam M, Badkoobeh A, Rahbar M, et al. Biomaterials in Guided Bone and Tissue Regenerations: An Update. Advances in Materials Science and Engineering. **2022**;2022:2489399. [Crossref], [Google Scholar], [Publisher]

[48] Nazari B, Amani L, Ghaderi L, Gol MK. Effects of probiotics on prevalence of ventilator-associated pneumonia in multitrauma patients hospitalized in neurosurgical intensive care unit: a randomized clinical trial. Trauma Monthly. **2020**; 25(6): 262-268. [Crossref], [Google Scholar], [Publisher]

[49] Birmangi S, A Review of the Effect of Corona on the Human Brain – Short Review, *Eurasian Journal of Chemical, Medicinal and Petroleum Research,* **2022**, 1 (3), 80-87 [Google Scholar], [Publisher]

[50] Margy S, A Review of the Effect of Brain imaging- Short Review, *Eurasian Journal of Chemical, Medicinal and Petroleum Research,* **2022**, 1 (3), 88-99 [Google Scholar], [Publisher]

[51] Musaei S, The Effect of Pregnancy on the Skin, *Eurasian Journal of Chemical, Medicinal and Petroleum Research*, **2023**, 2(1), 17-23. [Google Scholar], [Publisher]

[52] Nazardani SZ, et al., A comprehensive evaluation of the Sports Physiotherapy curriculum, *Eurasian Journal of Chemical, Medicinal and Petroleum Research*, **2023**, *2*, 10-16. [Google Scholar], [Publisher]

[53] Mahkooyeh SA, et al., Chemical laboratory findings in children with covid-19: A systematic review and meta-analysis, Eurasian Chemical Communications, **2022**, 338-346, [Crossref], [Google Scholar], [Publisher]

[54] Saliminasab M, Jabbari H, Farahmand H, Asadi M, Soleimani M, Fathi A. Study of antibacterial performance of synthesized silver

nanoparticles on Streptococcus mutans bacteria. Nanomedicine Research Journal. 2022 Oct 1;7(4):391-6.[Google Scholar], [Publisher]

[55] Ahmadi SE, et al., Succinct review on biological and clinical aspects of Coronavirus disease 2019 (COVID-19), Romanian Journal of Military Medicine, **2022**,356-365, [Google Scholar], [Publisher]

[56] Sarejloo SH, et al., Neutrophil-to-Lymphocyte Ratio and Early Neurological Deterioration in Stroke Patients: A Systematic Review and Meta-Analysis, **2022**, Article ID 8656864 [Crossref], [Google Scholar], [Publisher]

[57] Tahmasebi E, Alam M, Yazdanian M, Tebyanian H, Yazdanian A, Seifalian A, et al. Current biocompatible materials in oral regeneration: a comprehensive overview of composite materials. Journal of Materials Research and Technology. **2020**;9(5):11731-55. [Crossref], [Google Scholar], [Publisher]

[58] Tosan F, Rahnama N, Sakhaei D, Fathi AH, Yari A. Effects of doping metal nanoparticles in hydroxyapatite in Improving the physical and chemical properties of dental implants. Nanomedicine Research Journal. **2021**;1;6(4):327-36.[Crossref], [Google Scholar], [Publisher]

[59] Yazdanian M, Rahmani A, Tahmasebi E, Tebyanian H, Yazdanian A, Mosaddad SA. Current and Advanced Nanomaterials in Dentistry as Regeneration Agents: An Update. Mini Reviews in Medicinal Chemistry. **2021**;21(7):899-918. [Crossref], [Google Scholar], [Publisher]