



International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 4 Number 8 (August-2016) pp. 215-221

Journal home page: <http://www.ijcrar.com>

doi: <http://dx.doi.org/10.20546/ijcrar.2016.408.018>



Effect of 2 gr. intravenous Paracetamol in control of pain after gynecologic laparoscopic surgery

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KEYWORDS

Gynecologic Surgery,
Laparoscopy,
Acute Postoperative Pain,
Preventive Analgesia,
Paracetamol.

A B S T R A C T

Paracetamol is a non-opioid analgesic that causes analgesia by serotonergic mechanism of action and inhibiting prostaglandin synthesis in the central nervous system. The usual dose of Paracetamol is 1g every 6 hours; however, this dosage does not afford enough postoperative analgesia. This study compared the effectiveness of 2g Paracetamol to usual 1g dosage in controlling gynecologic laparoscopic surgical pain. In this double blind randomized clinical trial, 30 patients aged 20-70 years with ASA class I or II of laparoscopic gynecologic surgery were studied. At the end of surgery, the study group (15 cases), received 2 grams of Paracetamol and the control group (15 cases) received 1g Paracetamol in 100ml normal saline solution within 15 minutes. The prevalence of abdominal pain and shoulder pain in recovery in study group were 4.34% and 00% in the control group was 47.82% and 4.34%, respectively ($P < 0.001$ and $P = 0.013$). The mean abdominal pain score in recovery in study group (0.07 ± 0.33) was significantly lower than in control group (2.01 ± 1.62) ($p < 0.001$). The mean shoulder pain score in recovery in study group (0.00 ± 0.00) was significantly lower than in control group (1.53 ± 0.55) ($p < 0.018$). Time to request for the first analgesic in the study group was longer ($P = 0.03$). Liver tests in the 24 hours after surgery in both groups were not significantly different ($p > 0.05$). Prescription of Paracetamol 2g at the end of surgery, compared with 1gr dosage, can safely and effectively reduce the prevalence and scores of acute postoperative pain after gynecologic laparoscopic surgery.

Introduction

In recent years considerable advancement has been achieved in proper postoperative treatments due to the better understanding of pain physiology, discovery of new

pain killers with different impact mechanisms, and use of newer techniques of painkillers. The main objective of these efforts is to ensure safety, availability, ease

of prescription, and cost-effectiveness of post-operative painkiller prescriptions [1].

Acute postoperative pain is an unpleasant experience for patients, which results from surgical tissue damage. Pathophysiological responses to surgical damage can cause changes to cardiovascular, respiratory, digestive, and endocrine systems. In addition, ineffective treatment of acute postoperative pain is a chronic risk factor of postoperative pain [1-3].

Laparoscopy is an acceptable and reliable alternative to open surgery in many surgical procedures including women diseases. However, female patients undergoing laparoscopy experience less postoperative pain than open surgery. Moreover, patients complain about the pain of incision, insertion of trocars, lower abdominal pain, below-diaphragm pain, shoulder pain, and back pain. Post-laparoscopy pain may result from the volume of CO₂ gas remaining in the abdomen and intra-abdominal pain [4-6]. Paracetamol is a non-narcotic analgesic drug without many side effects of the aforementioned systemic drugs. Its analgesic side effect is associated with a serotonergic mechanism and inhibition of prostaglandin synthesis in CNS[7-11].

It also as leaves an antipyretic effect through inhibition of the COX-3 enzyme in the hypothalamus. It has no antiplatelet effect and is the best choice in the case of counter-indication in administration of NSAIDs or its ineffectiveness [12-14]. The normal dose of Paracetamol is 1 gram every 6 hours. Paracetamol has a hepatotoxicity potential that results from over 4-gram/day dosages and continuous use of the drug [15]. Research indicates that the common 1-gram dose of Paracetamol does not lead to adequate relief of pain after surgery [10, 16].

Effects of drugs are dose-dependent. In some studies, higher doses of drugs are used to control postoperative pain [16, 17]. The desirable dose of Paracetamol is not known and limited research has been conducted on administration of its higher doses.

The present double-blind clinical trial was carried out to compare effects of administration of 2 grams and 1 gram of Paracetamol 15 minutes before completion of surgery on post-laparoscopy pain in women.

Materials and Methods

In a double-blind clinical trial which was conducted in Tabriz on patients under women laparoscopy surgery from 2015 to 2016, the preventive analgesic effects of two different doses of venous Paracetamol on controlling post-laparoscopy pain were compared.

In this research, 30 women with an age of 20 to 70 years and ASA-I-III, who were candidates for diagnostic laparoscopic surgery or women operative laparoscopic surgery (with general anesthesia) were included in the research using the convenience sampling method and were randomly divided into the experiment and control groups.

After obtaining written consent of the Ethics Committee of the research deputy of Tabriz University of Medical Sciences as well as the written consent of patients, a total of 30 women with an age of 20 to 70 years and ASA (American Society of Anesthesiologists) I and II physical statuses, who were candidates for diagnostic laparoscopic surgery or gynecologic operative laparoscopy, were included in the research.

After entering the operation room, venous paths in patients were opened using IV 18. All patients were subjected to general anesthesia with 0.05 mg/kg Midazolam, 1-2 µg/kg Fentanyl, 1.5-2 mg/kg Propofol, and 0.5 mg/kg Atracurium using a properly-sized tracheal tube. Anesthesia was preserved by infusing 50-100 µg/kg per minute to protect depth of anesthesia. When necessary, Fentanyl was also injected at a dose equal to half of the initial dose.

All patients were subjected to controlled respiration for protection of an approximately 35 ± 5 mmHg CO₂ end-expiratory pressure. In all patients, liquids were properly replaced with crystalloid, and a standard monitoring procedure including pulse oximetry, ECG, non-invasive blood pressure, and capnography was conducted. Laparoscopy was carried out by two laparoscopists.

Fifteen minutes before completion of the surgery in the experiment group patients, 2 grams of Paracetamol was infused into 100 ml of normal saline serum within 15 minutes while 1 gram of Paracetamol was infused into 100 ml of normal saline serum within 15 minutes in the control group patients.

Following the surgery, a reversed effect muscle relaxant was injected reverse the remainder of the muscle relaxant and the tracheal tube was removed.

Patients were transferred to PACU and their vital signs were recorded. Intensity of shoulder pain and abdominal pain was recorded 6 and 24 hours after recording based on VAS in PACU.

Patients with pain scores of $4 \leq$, $4 >$, $2 \leq$, and $2 >$ received 0.5-1 mg/kg venous Pethidine, Tramadol, and Diclofenac suppository, respectively. Moreover, prescription of other

sedatives (oral acetaminophen) was also recorded.

The time of the first request for painkiller, total dose of postoperative analgesic drugs, side effects (including nausea, vomiting, drowsiness, and respiratory depression). Moreover, liver enzymes were measured after 24 hours.

Ethical Considerations

Written informed consent of all patients was obtained at the beginning of the research. Patients were also allowed to leave the research in any stage.

Statistical analysis

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean \pm SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

Results and Discussion

In this research, the analgesic effects of two doses of venous acetaminophen in women subject to laparoscopic surgeries were assessed.

The mean age of patients in the control and experiment groups was 31.84 ± 5.99 years and 30.08 ± 5.90 years, respectively (P=0.159).

These results suggest that prevalence of pain relief in the recovery (P<0.001) 6 hours (p=0.006) after the treatment in the experiment group was significantly higher

than the control group, but no significant difference was observed between results of the two groups in other time periods ($P>0.05$). Finding indicates that prevalence of pain relief in recovery ($P=0.013$) of patients of the experiment group was significantly higher than the control group, but no significant difference was observed between the two groups in other time periods ($P>0.05$).

In the control group, 40 patients asked for analgesic drugs, whereas in the experiment group 25 patients asked for analgesic drugs, and the difference was shown to be statistically significant using Pearson's test ($P=0.001$). The mean time of the first request for analgesic drugs in patients of the control and experiment groups was 2.29 ± 3 and 3.5 ± 3.6 hours, respectively. The times of the first request for analgesic drugs by patients of the two groups were compared using the Mann-Whitney test due to a lack of normal distribution, and the mean rank of patients of the control group was 28.98 with a total rank of 1159, whereas the mean rank of the experiment group was 39.44 with a total rank of 986. Hence, the difference was statistically significant ($P=0.03$, $U=339$).

Results of laboratory findings of patients indicate that there was no significant statistical difference between results of liver enzyme experiments on patients of the two groups ($P>0.05$).

Since a physician is required to reduce the pain of patients, relieving the pain of patients after surgeries is essential and vital. Studies have indicated that 30-40% of patients experience moderate to severe levels of pain following surgeries. The feeling of irritation, suffering, or distress caused by sensitivity of nerve endings is the result of an objective or subjective multifactor phenomenon influenced by

physiological, cultural, psychological, and social factors[18]. Numerous efforts have been made to reduce, control, or eliminate pain. The current treatment solutions for pain control during surgery or before/after it are mainly based on treatment with anti-narcotics and NSAIDs [19].

Acute postoperative pain management has undergone extensive evolutions in the past three decades [18], and it is one of the most important challenges that results in relief of patients and surgeons and facilitates release of patients from hospital. Postoperative pain is a classic and typical indication used in administration of systematic pain killers. Effective control of postoperative pain is an integral part of postoperative care [20-21].

The new pain management standards were proposed by CAHO in 2000, and anesthesiologists have always been on the front line of research in this field due to their knowledge of pharmacology and different regional pain killing techniques. These specialists are pioneers in evolution of postoperative acute pain services. Intensity of postoperative pain is an important predictor of chronic postoperative pain. Hence, control of acute postoperative pain can significantly contribute to facilitation of the short- and long-term postoperative convalescence [18].

Acetaminophen is an effective and low-risk drug, which has been recently used in most parts of the world including the Europe for treatment of mild to moderate pains. This drug has been recently introduced as a substitute for opioids for short-term analgesic treatment. Venous acetaminophen is a water-soluble drug with insignificant side effects. To study the effects of this drug on postoperative pain, a study was carried out on 101 patients with moderate to severe pain after orthopedic surgery by

administering 1 gram of acetaminophen or placebo every 6 hours for 24 hours. Analgesic treatment was carried out by controlling the patient with venous morphine. Venous acetaminophen was significantly more effective than the placement in reducing pain 15 minutes to 6 hours following operation.

The mean time for requesting the supplementary dose of morphine in the acetaminophen group and placebo group was 3 hours and 0.8 hours, respectively. The administered dose of morphine and placebo within 24 hours was 38.3 mg and 57.4 mg, respectively (33% decrease in consumption of morphine with acetaminophen) [22].

In our study, the mean time required for supplementary dose of other sedatives in the control and experiment groups was 2.29 ± 3 hours and 3.5 ± 3.6 hours, respectively. The mean doses of Pethidine, Tramadol, and Diclofenac suppository in the experiment group were 4.67 ± 9.68 , 23.91 ± 34.54 , and 60.87 ± 61.38 whereas the doses in the control group were 5.76 ± 10.49 , 27.17 ± 37.57 , and 95.65 ± 84.21 . Therefore, the levels were lower in all cases in the experiment group.

Numerous studies have been assessed so far. The peak effect of intravenous acetaminophen is one hour and its effect lasts for 4 to 6 hours [23-25].

Dejonckheere *et al.*, carried out a clinical trial on 80 patients to study the effects of venous acetaminophen and Tramadol on relieving pain after thyroidectomy. They found that pain relieving was more successful in the Tramadol group than the acetaminophen group, many patients in the Tramadol group experienced nausea and vomiting [24]. In the present research, shoulder pain and abdominal pain following

laparoscopy surgery were relieved more effectively with a higher dose of acetaminophen (2 gram) as compared to a lower dose (1 gram). Moreover, the levels of nausea and vomiting in the lower-dose acetaminophen group were higher.

Inal *et al.*, (2007) conducted a clinical trial titled "intravenous infusion of Paracetamol is better than intravenous infusion of Meperidine" on 50 patients and concluded that intensity of pain varied in the two pharmaceutical groups. Moreover, after administration of drugs, the intensity of pain in the Meperidine group peaked for two hours after the surgery, whereas in the acetaminophen group intensity of pain peaked 6 hours after the surgery. However, both groups displayed the same pharmaceutical side effects [26].

In a study by Babl *et al.*, in the Royal Hospital of Melbourne (Australia) in 2011, the effects of venous acetaminophen on relief of pain of patients in the emergency ward were studied and it was stated that intravenous administration of acetaminophen was effective for relieving the pain of patients and reduced the need for narcotic sedatives in these patients [27].

Wninger *et al.*, conducted a study in Phoenix University of Arizona (USA) in 2010 to study the effect of intravenous acetaminophen on relieving the abdominal pain of patients following surgery.

They stated that administration of intravenous acetaminophen in the patients significantly reduced their levels of pain [14]. In our research, administration of a single 2-gram dose of acetaminophen as compared to a single 1-gram acetaminophen was more effective in reducing abdominal and shoulder pain after laparoscopy.

Conclusion

Administration of 2grams of Paracetamol following surgery can effectively and safely reduce prevalence and scores of pain after gynecologic laparoscopic surgery as compared to 1 gram of Paracetamol.

Suggestions

For a better comparison of the effects of Paracetamol on the reduced use of narcotic sedatives and NSAIDs it is recommended to use one type of pain killer following surgeries in future studies.

Moreover, it is recommended to conduct more studies on the effects of higher dosages of Paracetamol on controlling postoperative pain in other surgeries.

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How to cite this article:

Simin Atashkhoei, Sadigheh Abdollahi Fard, Morteza Ghोजazadeh, Reza Kardan and Magsoud Eskandari. 2016. Effect of 2 gr. intravenous Paracetamol in control of pain after gynecologic laparoscopic surgery. *Int.J.Curr.Res.Aca.Rev.*4(8): 209-214.
doi: <http://dx.doi.org/10.20546/ijcrar.2016.408.018>