The Analgesic Effect of Pre-Operatively Administered Combination of Dexamethasone and Tramadol on Post-Operative Pain in Patients Undergoing Open Appendectomy- Randomized Clinical Trial

Muhammad Nauman Zafar [1], Ubair Ullah Shaheen [2], Rafay Ali Khan [2], Ammar Zaman Khan [3]

ABSTRACT

OBJECTIVE: To compare the analgesic effect of pre-operatively administered combination of dexamethasone and tramadol versus tramadol only on post-operative pain scores of patients undergoing open appendectomy.

STUDY DESIGN: A Randomized, double-blinded, parallel group study.

PLACE AND DURATION: Study was carried out in Accident and Emergency Department of Benazir Bhutto Hospital, Rawalpindi from 1st February 2017 to 27th March 2017.

METHODOLOGY: Patients undergoing open appendectomy were enrolled using the inclusion criteria and interventional protocol was randomized across two parallel groups; 1st group received pre-operative intravenous combination of dexamethasone and tramadol and the 2nd group received tramadol only. The pharmacological variables of anaesthesia were kept at a constant level for all the participants of the study. Pain was assessed at 0-4 hours post-operatively using the Numeric Rating Scale (NRS).

RESULTS: There were 32 patients in 1st group (combined dexamethasone tramadol) and 30 patients in 2nd group (tramadol only). Mean post-operative pain score(as per NRS) at 0-4 hours was 3.06 in group 1 while it was 4.53 in group 2 (p value=0.002) Among the 1st group, a remarkable 65.6% had only mild pain(NRS 1-3) and 34.3% had moderate pain(NRS 4-6). Among the 2nd group, 30% had mild pain, 53.3% had moderate pain, while 16.6% of the patients had severe post-operative pain (NRS 7-10). Regarding rescue analgesia, only 34.3% of combined dexamethasone tramadol group had to be administered additional post-operative analgesia.

CONCLUSION: Pre-operative administration of a combination of intravenous dexamethasone and tramadol results in statistically significant lesser pain scores and decreased requirement of rescue analgesia at 0-4 hours post-operatively in patients undergoing open appendectomy for acute appendicitis.

KEY WORDS: Acute Appendicitis, Open Appendectomy, Post-Operative Pain, Analgesia, Dexamethasone, Tramadol

HOW TO CITE THIS:

Zafar MN, Shaheen UU, Khan RA, Khan AZ. The Analgesic Effect of Pre-Operatively Administered Combination of Dexamethasone and Tramadol on Post-Operative Pain in Patients Undergoing Open Appendectomy- Randomized Clinical Trial. Isra Med J. 2018; 10(1): 36-39

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

During the 21st century, the pooled incidence of acute appendicitis (in per 100,000 person-years) was 100 in North America, and the estimated cases in 2015 was 378,614. The pooled incidence ranged from 105 in Eastern Europe to 151 in Western Europe [1]. Post-operative pain after appendectomy is one of the commonest complication experienced by the patients, which leads to the use of multiple oral and parenteral analgesics by patients and hospital setups [2,3], resulting in significant stress for patients and families and considerable financial burden, along with delay in returning to daily work routines[4]. Dexamethasone has an established role in alleviating post-operative pain scores when administered pre or per-operatively on the surgical floors due to their anti-inflammatory actions[5-8]. Their mechanism of action is by binding to specific receptors within the cytoplasm of targeted cells. The receptor-steroid (dexamethasone) complex then moves into the nucleus, binding to DNA and altering synthesis of specific proteins, including inflammatory autacoids and immune-linked cytokines[9,10]. Tramadol is a centrally acting synthetic opoid analgesic, which acts by binding to μ-opioid receptor as well as by inhibiting the re-uptake of serotonin and norepinephrine [11,12]. Onset of action after intravenous administration is almost immediate and lasting for about 4-6 hours [13,14]. Multimodal analgesia describes using different analgesic agents with different mechanisms and sites of action, consequently leading to the use of lower doses of drugs and avoiding unwanted adverse effects[15-19], along with superior analgesia experienced by patients. In this study protocol, one

1. Resident Physician, Medicine Unit-1, Holy Family Hospital, Rawalpindi.
2. House Officer, Surgery Unit-1, Benazir Bhutto Hospital, Rawalpindi.
3. Resident Surgeon, Surgery Unit-1, Benazir Bhutto Hospital, Rawalpindi.

Correspondence to:
Dr. Muhammad Nauman Zafar
Resident Physician, Medicine Unit-1, Holy Family Hospital, Rawalpindi.
Email : nouman7235@gmail.com

Received for Publication: 22-08-17
Accepted for Publication: 14-02-18

group were given the combination of 8mg IV dexamethasone and 50mg IV tramadol 15 minutes before induction of general anaesthesia and the second group received only 50 mg IV tramadol. Post-operative pain was assessed at 0-4 hours post-operatively using the Numeric Rating Scale (NRS). It was hypothesized that patients undergoing open appendectomy with pre-operative intravenous administration of combined 8mg dexamethasone and 50mg tramadol will have statistically significant lower pain scores as compared to patients administered 50mg intravenous tramadol only. Requirement of any rescue analgesia during the post-operative period was observed and documented for each of the subject. The objective of this study was to compare the analgesic effect of pre-operatively administered combination of dexamethasone and tramadol versus tramadol only on post-operative pain in patients undergoing open appendectomy

METHODOLGY

This double-blinded, randomized, parallel-group study with balanced randomization (1:1) was approved by IRF (Institutional Research Forum) and research ethical review committee of Rawalpindi Medical College and Allied Hospital. The study setting was Accident and Emergency Department of Benazir Bhutto Hospital, Rawalpindi, Pakistan and duration was 1st February 2017- 27th March, 2017. Study population was patients undergoing open appendectomy, at the aforementioned setting, as advised per duty surgeon. Inclusion criteria was adult patients(aged 18 years or older) undergoing open appendectomy, ASA category 1-2, who gave written consent to the study intervention and have histopathologically proven acute appendicitis, performed on the appendix sample post-operatively. Exclusion criteria was patients not able to report their pain scores, patients using systemic or oral steroids or immunosuppressive agents, pregnant or lactating mothers, diabetic patients or patients with a known sensitivity/allergy to tramadol. Assuming a difference in means of 9 with a standard deviation of 22.35 on NRS, according to a study reporting post-operative pain scores of patients undergoing appendectomy [20], an alpha level of 0.05 and power of 80% using comparison of 2 means with a 5% superiority margin, we required 32 patients per group, making the total sample size of 64 patients. After diagnosing cases of acute appendicitis and obtaining their verbal and written consents, they were assigned into their respective groups and received treatment protocol according to a computer generated randomization schedule, which listed the allocation sequences assigned to each of the two intervention groups (combined dexamethasone and tramadol group "CDT" and tramadol only group "T"). The patients were given the treatment by one of the investigator who administered prepared injections containing the drugs (blinded to treatment sequence), prepared by a nurse who was aware of the randomization schedule and was not part of the rest of the study. Intervention was with either 8mg of dexamethasone plus 50mg tramadol or 50mg tramadol only, both diluted to make a total of 5ml injection and labelled with an allocation sequence/code. The pharmacological variables of anaesthesia were kept at a constant level for all the participants of the study. As per policy of aforementioned hospital, TIVA (total intravenous anaesthesia)[21] was used for induction, and isoflurane and nitrous oxide were used as maintenance gases, each of them optimized at a constant level for all patients. Throughout the study, the patients and investigators involved in study were blinded to the intervention assignments. Primary outcome was post-operative pain assessed at 0-4 hours post-operatively, using the Numeric Rating Scale (NRS)[22]. Patients with post-op GCS 15/15 were asked to rate their pain scores on a scale 0f 0-10, with 0 being no pain, and 10 being the worst possible pain. Secondary outcome was requirement of any post-operative RESCUE ANALGESIA, which was usually 50mg intravenous tramadol, unless contraindicated. Those cases were considered for rescue analgesia who either had NRS scores of ≥4 or who specifically requested for it. Cases in which post-operatively performed histopathology failed to document acute appendicitis were excluded from the study. Patients with per-operatively discovered perforated appendix were also not taken into consideration.

RESULTS

Using the inclusion criteria, a total of 82 patients were enrolled in the study, after getting their consent, against our required sample size of 64. Among them, post-operative histopathology report of 11 patients showed appendix to be non-inflamed, while 9 of the patients had perforated appendix discovered per-operatively, these cases were excluded from our study as per exclusion criteria, leaving 32 patients in CDT(1st group) and 30 in T (2nd group), a total of 62 patients. Mean post-operative pain scores at 0-4 hours post-operatively was 3.06 in CDT group (Combined Dexamethasone Tramadol) while it was 4.53 in the T group (Tramadol only) as per Numeric Rating Scale (NRS), with the independent sample t-test showing p vaue to be 0.002 (statistically significant) (Table - II).

65.6% of CDT group had only mild pain(NRS 1-3) and 34.3% had moderate pain(NRS 4-6). In the Tramadol only group, 30% had mild pain, 53.3% had moderate pain, while a further 16.6% had a severe pain(NRS 7-10) post-operatively. Regarding the need for additional post-operative analgesia, 70% of the T group(21 out of 30) patients required rescue analgesia in the form of 50mg IV tramadol injection, while only 34.3% of CDT group(11 out of 32 patients) had a need for any post-operative analgesia.

Table – I: MEAN POST-OPERATIVE PAIN SCORES (0-4 HOURS) as per NRS (N=62)

Groups	Drug (pre-operative administration)	No. of cases (n)	Mean
Group - 1	Dexamethasone + tramadol	n=32	3.0625
Group - 2	Tramadol only	n=30	4.5333

DISCUSSION

Previously, a few clinical trial had been carried out to determine the role of dexamethasone in patients undergoing appendectomy [23,24]. These studies failed to deduce any statistically signif-

Table - II: PAIN INTENSITY COMPARISON (NRS) (N=62)

Groups	Drug (pre-operative administration)	Grading	0-4 hours post-operatively
Group - 1	Combined dexamethasone,tramadol group(CDT) (n=32)	No pain(NRS 0)	0
		Mild(NRS 1-3)	21(65.6%)
		Moderate(NRS 4-6)	11(34.3%)
		Severe(NRS 7-10)	0
Group - 2	Tramadol only group (T) (n=30)	No pain(NRS 0)	0
		Mild(NRS 1-3)	9(30.0%)
		Moderate(NRS 4-6)	16(53.3%)
		Severe(NRS 7-10)	5(16.6%)

icant analgesic effect of dexamethasone post-operatively. This result might be in part due to the fact that their exclusion criteria did not include perforated appendix, which has a higher post-operative pain score as compared to inflamed appendix only[25]. In contrast, in this double-blinded, randomized clinical trial, only those patients were taken into consideration having histopathologically proven inflamed, non-perforated appendix. The concept of pre-operatively administered multimodal analgesia for patients undergoing open appendectomy is introduced in this study, and hypothesis was structured that patients receiving combined dexamethasone and tramadol will have statistically significant lower pain scores at 0-4 hours post-operatively. During this post-operative period, it was ensured that patients do not receive any prophylactic analgesia, unless there was a clear indication. As per results, there is a statistically significant(p value= 0.002) difference in mean pain scores (as per NRS) between the CDT (combined dexamethasone tramadol) and T (tramadol only) groups, thereby patients in the CDT group had lower pain scores, measured at 0-4 hours post-operatively, reason being the analgesic role of dexamethasone and the concept of multimodal analgesia, which proves that if two analgesics with different mechanisms and sites of actions, are given simultaneously, their combined action is significantly superior as compared to one of the analgesic agent given alone and have a lesser adverse effects profile. 65.6% patients of the CDT reported mild pain, while only 30% of the T group patients had mild pain (NRS 1-3) post-operatively; 34.3% of CDT population and a remarkable 53.3% of the T group patients resided in the category of moderate pain (NRS 4-6), consequently, more than half of the patients receiving only pre-operatively 50mg tramadol reported moderate pain post-operatively, resulting in significant distress. Further, 16.6% patients from T group had severe pain (NRS 7-10), while no patient from CDT group reported severe post-operative pain. These figures clearly highlight the superior analgesic role of dexa and multimodal analgesia. The role of dexamethasone in patients undergoing open appendectomy is further clarified by the requirement of patients of any post-operative rescue analgesia. Only 34.3% patients from CDT group had a need for rescue analgesia; a significant 70% patients from tramadol group had to be administered post-operative analgesia to relieve them of their pain. Rescue analgesia, in itself, is a significant burden for patients and hospital setups, and the pain alleviating effect of dexamethasone is clearly shown by these aforementioned figures. In view of the results, 8mg dexamethasone has a statistically significant analgesic effect when given pre-operatively in a multimodal analgesic regimen, which might lead to an early return of the patient to daily work routine and a considerably lesser psychological and financial burden on the affected population. Its role, however, in cases of perforated appendix, could still be worked upon. This study only focused on open appendectomy procedures. Before making the multimodal analgesic regimen of dexa and tramadol as a standard protocol in acute appendicitis, its efficacy and adverse effect profile should also be extensively investigated in the emerging laparoscopic appendectomy procedures as well.

CONCLUSION

Pre-operative administration of a combination of intravenous dexamethasone and tramadol results in statistically significant lesser pain scores and decreased requirement of rescue analgesia at 0-4 hours post-operatively in patients undergoing open appendectomy for acute appendicitis.

CONTRIBUTION OF AUTHORS

Zafar MN: Conception and design of study, data analysis and manuscript writing
Khan RA: Manuscript drafting, data compilation and analysis
Shaheen UU: Final critical review of manuscript
Zaman A: Data collection and compilation, literature review

Disclaimer: None.
Conflict of Interest: None.
Source of Funding: None.

REFERENCES

1 Ferris M, Quan S, Kaplan BS, Molodecky N, Ball CG, Chernoff GW, et al. The global incidence of appendicitis: A systematic review of population based studies. Ann Surg 2017; 266: 237-41.
2 Hyung OK, Chang HY, Sung RL, Wion M, Rom MG, Leo JK et al. Pain after laparoscopic appendectomy: A comparison. J Korean Surg Soc 2012; 82: 172-78.
3 Behdad A, Hosseinpour M, Khorasani P. Preemptive use of ketamine on post operative pain of appendectomy.

Korea J Pain 2011; 24: 137-40.
4 Li P, Xu Q, Ji Z, Gao Y, Zhang X, Duan Y, et al. Comparison of surgical stress between laparoscopic and open appendectomy in children. J Paeds Surg 2005; 40: 1279-83.
5 Ahmad RM, Sholeh N, Amir S, Akhondzadeh R. The effect of single dose administration of dexamethasone on post operative pain in patients undergoing laparoscopic cholecystectomy. Anaesth & Pain Med 2014; 4: 140-42.
6 Moyano J, Garcia M, Caicedo M. Analgesic effect of Dexamethasone after arthroscopic knee surgery: A randomized controlled trial. Pain Res & Mang 2016; 10: 120-28.
7 Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2012; 110: 191-200.
8 Desmet M, Braems H, Reynvoet M, Plasschaert S, Cauwelaert JV, Pottel H, et al. IV and perineural dexamethasone are equivalent in increasing the analgesic duration of a single-shot interscalene block with ropivacaine for shoulder surgery: a prospective, randomized, placebo-controlled study.Br J Anaesth. 2013; 111: 445-52.
9 Becker DE. Basic and clinical pharmacology of glucocorticosteroids. Anesth Prog 2013; 60: 25-32.
10 Jaegar P, Grevstad U, Nielsen K, Sauter AR, Sorenson JK, Dahl JB. Does dexamethasone have a perineural mechanism of action? A paired, blinded, randomized, controlled study in healthy volunteers. Br J Anaesth. 2016; 117: 635-41.
11 Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2012; 5: 431-38.
12 Minami K, Ogata J, Uezono Y. What is the main mechanism of tramadol. Arch Pharma 2015; 388: 999-1007.
13 Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2012; 110: 191-200.
14 Kaneko K, Umehara M, Homan T, Okamoto K, Oka M, Oyama T. The analgesic effect of tramadol in animal models of neuropathic pain and fibromyalgia. Neuroscience letters 2014; 562: 28-33.
15 Reddi D, Curran N, Stephens R. An introduction to pain pathways and mechanisms. Br J Hosp Med 2013; 74: 188-91.
16 Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesth 2009; 22: 588-93.
17 Trabulsi EJ, Patel J, Viscusi ER, Gomella LG, Lallas CD. Preoperative multimodal pain regimen reduces opoid analgesia for patients undergoing robotic assisted laparoscopic radical prostatectomy. Uro 2010; 76: 1122-24.
18 Gritsenko K, Khelemesky Y, Kaye AD, Vadivelu N, Urman RD. Multimodal therapy in perioperative analgesia. Best pract & Res Clinic Anaesth 2014; 28: 59-79.
19 Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. Curr Opin Anesth 2010; 23: 697-703.
20 Kleif J, Kirkegaard A, Vilandt J, Gogenur I. Randomized clinical trial of preoperative dexamethasone on postoperative nausea and vomiting after laparoscopy for suspected appendicitis. Br J Surg 2017; 104: 384-92.
21 Henrik E, Johann R. Total intravenous anaesthesia techniques for ambulatory surgery. Curr Opin Anaesth 2009; 22: 725-29.
22 Cleland JA, Childs JD, Whitman JM. Psychometric properties of the Neck Disability Index and Numeric Pain Rating Scale in patients with mechanical neck pain. Arch Phy Med & Rehab 2008; 89: 69-74.
23 Kleif J, Kirkegaard A, Vilandt J, Gogenur I. Randomized clinical trial of preoperative dexamethasone on postoperative nausea and vomiting after laparoscopy for suspected appendicitis. Br J Surg 2017; 104: 384-92.
24 Qi YU, Qing C. Effect of ondansetron and dexamethasone preventing side effects during appendectomy. China J Med 2004; 29: 110-15.
25 Yau KK, Siu WT, Tang CN. Laparoscopic versus open appendectomy for complicated appendicitis. J Am Coll Surg 2007; 205: 60-65.