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Research Article

The Effect of Intraoperative Diphenhydramine/Morphine on Acute Pain and Opioid Consumption after Spine Surgery

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ABSTRACT

Background: One of the most common problems after spine surgery is very severe pain that usually affects outcome of patients after surgery and duration of hospital stay. Acute postoperative pain has several mechanisms, and multimodal analgesia by different mechanism of action will help control to it. In this study, we intended to investigate the effect of intravenous diphenhydramine injection during induction of anesthesia and morphine before incision on the control of acute pain in postoperative laminectomy.

Methods: 130 patients scheduled for spine surgeries were assigned to receive a single pre induction dose of diphenhydramine 0.4mg/kg IV (D group) and morphine 0.15mg/kg before incision in addition acetaminophen 1gr IV at the end of surgery and just morphine 0.15mg/kg and acetaminophen 1gr IV (C group) in a randomized, double-blind trial. Postoperative pain, analgesic requirements in recovery and 24 hr after surgery were assessed.

Results: The mean pain intensity in recovery was lower in the diphenhydramine group than in the control group (MD, 2.13; 95% confidence interval (CI), 1.72–2.53; $P < .0001$) and the need for analgesia was much lower in the diphenhydramine group than in the control group. $P < 0.001$. The severity of pain and the need for analgesics in the diphenhydramine group had a significant decrease in the ward compared to the control group.

Conclusion: Prophylactic diphenhydramine 0.4 mg/kg at induction of general anesthesia in combination with morphine 0.15mg/kg before incision and acetaminophen 1gr at the end of surgery reduced the postoperative severity of acute pain and opioids requirement in the early postoperative period after spine surgeries.

Lumbar laminectomy is commonly performed in patients with lumbar spinal stenosis to relieve low back pain, reduce radiculopathy and improve overall function. Effective pain control improves post-operative outcomes and patient satisfaction and inadequate pain management is one of the main reasons for delayed discharge or dissatisfaction after surgery [1-2]. Multimodal analgesia has frequently been recommended for enhanced recovery after surgery and reduction of postoperative complication [3].

Postoperative pain following spinal surgeries is due to activation of various pain mechanisms including nociceptive, neuropathic, and inflammatory [4].

The intensity of postoperative pain is directly proportional to the number of vertebrae involved in the surgery [5]. Peripheral as well as central sensitization further contributes to the development of increased pain.

In our previous study, combination of intraoperative ketamine-magnesium as a multimodal analgesia reduced

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the severity of acute pain and opiate consumption in the 48-h postoperative period after spine surgery [6].

Diphenhydramine is an antihistamine, by central sedative effects, which may potentiate the analgesic and sedative effects of narcotics [7].

Prophylactic administration of diphenhydramine provided smooth emergence from anesthesia. It reduced postoperative acute pain and improved quality of recovery after orthogenetic surgery [8].

In this clinical trial we hypothesized that preemptive injection of diphenhydramine and morphine during induction of anesthesia before incision would reduce postoperative acute pain in adult patients undergoing spine surgeries and it may also reduce opioid requirement and improve quality of recovery.

Methods

After approval by the Ethical Board Committee of Anesthesiology Department of Tehran University of Medical Sciences (TUMS), IR.TUMS.MEDICINE. REC.1398.140, this prospective randomized controlled study was conducted on130 patients in an academic center affiliated to TUMS in 2019-2020. Inclusion criteria were all adults' patients suffering lumbar canal stenosis and candidate for lumbosacral spine surgeries between 30-70 years old. Exclusion criteria were any history of closed angle glaucoma, uncontrolled psychiatric disorder and continued drug abuse.

In the operating room patients were randomly assigned to 1 of 2 groups: patients in group (D) received 0.4mg/kg Diphenhydramine, and patients in group C received normal saline.

To randomize patients who are candidates for surgery with inclusion criteria, block balanced randomization is used. Before studying, one of the persons who is not a member of the research team performs the randomization process by using Random generator software, forms four blocks for the intervention and control group. The complete cards of the four blocks are given to the head of the operating room, who is unaware of the study, in an envelope. A card is given to the patient after patient entrance to operating room and opened immediately before study drug or placebo administration. Patients unaware of study protocol and anesthesiologist and surgeon also unaware of kind of solution was injected. The study drug and placebo were already prepared (diluted in NaCl 0.9% to a total amount of 5 ml) and were indistinguishable and coded with the randomization number by the anesthesia nurse every day.

After standard monitoring, and before induction of anesthesia diphenhydramine 0.4mg/kg diluted in 5ml syringe (1ml = 10mg) was injected intravenously (IV) in D group and in the C group, the same volume of 5 ml normal saline was injected. Anesthesia induction was the same in both groups, by using midazolam 0.04 mg/kg, fentanyl 2 μg/kg, lidocaine 0.5 mg/kg, propofol 1-1.5 mg/kg, and atracurium 0.5 mg/kg. Continuous infusion of remifentanil 0.1-0.2 μg/kg/hour and inhalation of isoflurane was maintained during the anesthesia period to maintain anesthesia. Before incision, all patients receive a single dose 0.15mg/kg morphine sulfate slowly intravenously within three minutes.

Paracetamol 1 gr was infused 15min before extubation. At the end of surgery and reversal of muscle relaxant by neostigmine 30 μg/kg and atropine 10 μg/kg, extubation was performed when patients began adequate breathing spontaneously. After extubation and transferring of patients to the post anesthesia care unit (PACU), an anesthesiologist and nurse unaware of the study objectives, observed the patients.

The primary endpoint of the study was the evaluation of pain intensity based on the VAS score, no pain (0–4), mild pain (5-6), moderate pain (7–8), and severe pain (9–10) in the recovery period and the first 24 hours after transferring the patients to the ward. When VAS was≥4 or if patients requested analgesics morphine 2-4 mg was used as rescue analgesia in recovery period. During the first 24 h, a standard analgesic regimen of paracetamol 1 g was given intravenously every 8 h to all patients. In addition, pain assessment in the ward was performed by nurses every 6 h and titrated doses of morphine (2 mg bolus at 5 min intervals) were given if patients reported pain. Total opioids requirement during first 24 hours after surgery was also recorded.

Statistical analysis

Based on the results of Loftus et al's a clinical trial [9] and using 95% of the confidence level, 90% of power, and at least one mean pain score difference between the two groups, the sample size was estimated to be 65 patients in each of the two groups.

Demographic data was analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Data is presented as mean with standard deviation or frequency. Pearson's chi-square or Fisher's exact test was used to assess nominal variables across groups. Independent-sample t test was used to assess differences between groups. Finally, P values less than 0.05 were considered statistically significant.

Results

In this study, 130 patients were eligible and enrolled but only 129 were randomized into the Diphenhydramine (N= 65) and control (N= 64) groups and completed the study protocol (Figure 1).

Baseline characteristics of patients were similar between the two groups (Table 1). All patients underwent a kind of spine surgery.

The severity of pain score in the immediate postoperative period at PACU was lower in group D in compare to C group (MD, 2.13; 95% confidence interval (CI), 1.72–2.53; P < .0001) and total analgesic requirement was also reduced in this groups (MD, 3.79; 95% CI 2.99–5.84 lower; P < .0001), (Table 2). During the first 24 hours after surgery, the pain intensity was lower in the Diphenhydramine group and in proportion the need for analgesia was also reduced in this group.

Figure1- Study flow Diagram: D, Diphenhydramine; C, Control with normal saline

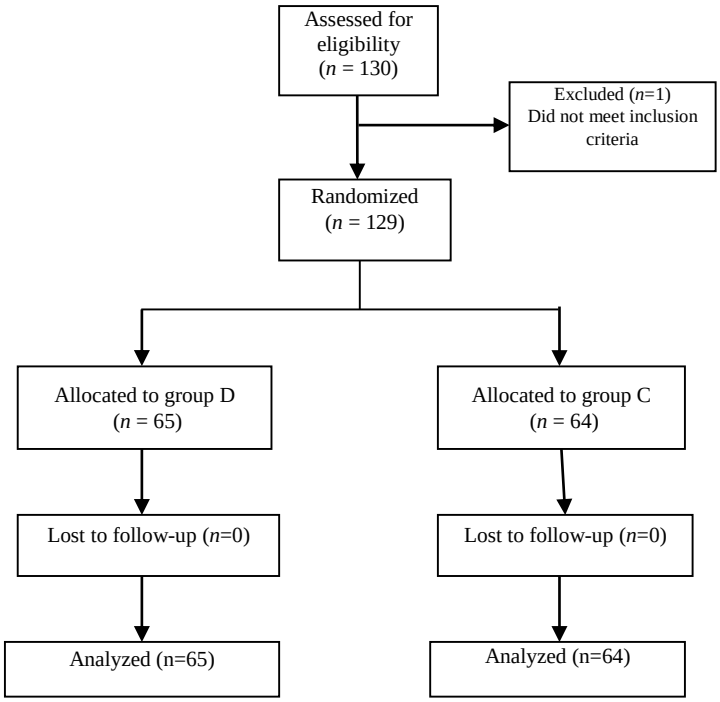

Table 1- Demographic data and perioperative outcome of patients

Variable	Intervention	control	P value
Gender(male/female)	38/32	40/30	0.1
Age(yr)	49.09±6.5	51.10±9.3	0.2
Duration pain before operation month	14.56±6.8	13.39±5.9	0.2
Severity of pain before operation (VAS)	7.3±1.2	6.9±1.8	0.2
weight	78.40±5.7	79.60±8.2	0.4
Duration operation	187.07±11.2	204.21 ±12.3	0.05

*Mean ± SD was reported for age, pain and weight, and n (%) was reported for gender
#Statistics: unpaired t-test or chi-square test, as appropriate

Table 2- Postoperative mean severity of pain and morphine requirement

Variable	Diphenhydramine (N = 65)	Control (N = 64)	P value
PACU VAS (1-min)	3.42±1.21	5.55±1.17	0.03
PACU VAS (20-min)	1.77±0.73	2.88±0.94	0.2
Morphine (mg in PACU)	3.12±0.23	6.29±1.45	0.0٠4
PACU(Duration-min)	65.12±6.3	77.23±5.8	0.003
Ward VAS 6-hr	2.11±0.2	3.16±1.2	0.005
Ward VAS 12-hr	1.11±1.5	3.11±1.2	0.005
Ward VAS 18-hr	2.61±1.3	2.87±1.4	0.6
Ward VAS 24-hr	2.41±1.3	2.67±1.1	0.5
Morphine, total mg/24	15±2.5	23±37	0.0٠2

*mean ± SD was reported for pain, fentanyl, VAS: Visual Analogue Scale. PACU: post-anesthesia care unit
Statistics: unpaired t test or Chi square test, as appropriate

Discussion

According to the preliminary results of this study, administration of diphenhydramine at the beginning of induction of anesthesia in lumbar spine surgeries can reduce severity of acute pain, in the early postoperative period. It also improves sedative condition of patents in the post anesthesia care unit. We also noted a significant reduction in the requirement for opioid pain medication at the early postoperative period ($p < 0.001$).

Multimodal analgesia can be achieved by combining different analgesics and different methods of administration, to provide better analgesia synergistically compared with conventional analgesia [10].

Diphenhydramine as an antihistamine was used orally and parentally in humans with the elimination half-life range between 2.4 and 9.3 hours in healthy adults [11]. It crosses the blood–brain barrier and its effects on central H1 receptors cause sedation, and has antiemetic activity by blocking H1 receptors in the area postrema and vomiting centre in the vestibular nucleus. Furthermore, diphenhydramine has anticholinergic properties that blocks muscarinic receptors at the same sites that may help in its antiemetic activity [12].

The main finding in the present study was that intraoperative administration of diphenhydramine resulted in less pain and analgesics requirements in recovery and early postoperative period.

Spinal procedures are generally associated with intense pain in the postoperative period, especially for the initial few days. Multidisciplinary adequate pain management in this period correlated with improved functional outcome, early ambulation, early discharge, and preventing the development of chronic pain [13].

Surgical-induced injuries release inflammatory mediators and histamine, which stimulate peripheral and central pain receptors and increases pain symptoms. Inhibition of histamine receptor signaling predominantly causes neuroprotective and antinociceptive effects [14]. In many clinical trials, the analgesic activity and local anesthesia of antihistamines have been expressed and their use has been described as an adjunct [15-16].

For example, Pourfakhr et al. studied 80 morbid obese patients undergoing laparoscopic sleeve gastrectomy and founded preoperative administration of diphenhydramine 0.4mg/kg reduced postoperative acute pain nausea/vomiting and morphine consumption compared to placebo [17].

Yu‐Yu Li et al. studied 96 adult female patients scheduled for elective gynecologic laparoscopic surgery and founded preoperative administration of diphenhydramine reduced the incidence and severity of postoperative bladder discomfort without significant side effects [18].

Limitation of the study include pain control protocol of these patients that was based on opioids, morphine with low titre doses and slow injection under monitoring in the first 24 hours of surgery and we didn't assess pain in prolonged time. After this study, addition of diphenhydramine reduced opioid use therefore its use was added to the treatment protocol at the beginning of anesthesia. In the following study, it is recommended to add a non-opioid analgesic such as NSAIDs to this preoperative drug combination and use it to control pain in the postoperative period.

Conclusion

Prophylactic diphenhydramine 0.4 mg/kg at induction of general anesthesia in combination with morphine 0.15mg/kg before incision resulted in lower severity of pain and less use of analgesic medications in the first 24 hours after lumbar spine surgeries.

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References

[1] Elsharydah A, Duncan KL, Rosero EB, Minhajuddin A, Somasundaram A, Joshi GP. Readmission rate after 2-level lumbar decompression: a propensity-matched cohort study comparing inpatient and outpatient settings. Clin Spine Surg. 2021; 34(1):E1-6.

[2] Pendharkar AV, Shahin MN, Ho AL, Sussman ES, Purger DA, Veeravagu A, et al. Outpatient spine surgery: defining the outcomes, value, and barriers to implementation. Neurosurg Focus. 2018; 44(5):E11.

[3] Joshi GP, Kehlet H. Postoperative pain management in the era of ERAS: an overview. Best Pract Res Clin Anaesthesiol. 2019; 33(3):259-67.

[4] Bajwa SJ, Haldar R. Pain management following spinal surgeries: an appraisal of the available options. J Craniovertebr Junction Spine. 2015; 6(3):105.

[5] Khajavi M, Asadian M, Imani F, Etezadi F, Moharari R, Amirjamshidi A. General anesthesia versus combined epidural/general anesthesia for elective lumbar spine disc surgery: A randomized clinical trial comparing the impact of the two methods upon the outcome variables. Surg Neurol Int. 2013; 4:105.

[6] Etezadi F, Farzizadeh M, Sharifinia HR, Alimohammadi M, Khajavi MR. The Effect of Intraoperative Ketamine and Magnesium Sulfate on Acute Pain and Opioid Consumption After Spine Surgery. Acta Medica Iranica. 2020; 221-4.

[7] Obara I, Telezhkin V, Alrashdi I, Chazot PL. Histamine, histamine receptors, and neuropathic pain relief. Br J Pharmacol. 2020; 177(3):580-99.
[8] Khajavi MR, Saffarian A, Majidi F, Moharari RS, Pourfakhr P, Parhiz SA. Prophylactic administration of diphenhydramine/ paracetamol reduced emergence agitation and postoperative pain following maxillofacial surgeries: a randomized controlled trial. Eur Arch Otorhinolaryngol. 2021.
[9] Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010; 113(3):639-46.
[10] Klimek M, Ubben JF, Ammann J, Borner U, Klein J, Verbrugge SJ. Pain in neurosurgically treated patients: A prospective observational study. J Neurosurg. 2006; 104(3):350-9.
[11] Obara I, Telezhkin V, Alrashdi I, Chazot PL. Histamine, histamine receptors, and neuropathic pain relief. Br J Pharmacol. 2020 Feb;177(3):580-99.
[12] Santiago-Palma J, Fischberg D, Kornick C, Khjainova N, Gonzales G. Diphenhydramine as an analgesic adjuvant in refractory cancer pain. J Pain Symptom Manage.2001; 22(2):699–703.
[13] Jones DB, Abu-Nuwar MR, Ku CM, Berk LA, Trainor LS, Jones SB. Less pain and earlier discharge after implementation of a multidisciplinary enhanced recovery after surgery (ERAS) protocol for laparoscopic sleeve gastrectomy. Surg Endosc. 2020: 34(12): 5574-5582.
[14] Simons KJ, Watson WT, Martin TJ, Chen XY, Simons FE. Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. J Clin Pharmacol. 1990; 30(7):665-71.
[15] Panula P, Nuutinen S. The histaminergic network in the brain: basic organization and role in disease. Nat Rev Neurosci. 2013; 14(7):472-87.
[16] Simons FE. Advances in H1-antihistamines. N Engl J Med. 2004; 351(21):2203-17.
[17] Pourfakhr P, Aghabagheri M, Zabihi Mahmoudabadi H, Najjari K, Talebpour M, Khajavi MR. Prophylactic Administration of Diphenhydramine/Acetaminophen and Ondansetron Reduced Postoperative Nausea and Vomiting and Pain Following Laparoscopic Sleeve Gastrectomy: a Randomized Controlled Trial. Obes Surg. 2021; 31(10):4371-4375.
[18] Li YY, Zeng YS, Chen JY, Wang KF, Hsing CH, Wu WJ, et al. Prophylactic diphenhydramine attenuates postoperative catheter-related bladder discomfort in patients undergoing gynecologic laparoscopic surgery: a randomized double-blind clinical study. J Anesth. 2020; 34(2):232-237.