Dexmedetomidine infusion prevents significant postoperative pain in the first 24 hours after myomectomy laparoscop....

Article *in* Acta poloniae pharmaceutica · January 2018

CITATIONS
0

READS
32

3 authors, including:

Bushra Hadi
Al-Ahliyya Amman University /Amman, Jord...
6 PUBLICATIONS **24** CITATIONS
SEE PROFILE

Ashok K. Shakya
Al-Ahliyya Amman University
103 PUBLICATIONS **722** CITATIONS
SEE PROFILE

Acta Poloniae Pharmaceutica – Drug Research, Vol. 75 No. 1 pp. 183–188, 2018 ISSN 0001-6837
Polish Pharmaceutical Society

PHARMACOLOGY

DEXMEDETOMIDINE INFUSION PREVENTS SIGNIFICANT POSTOPERATIVE PAIN IN THE FIRST 24 HOURS AFTER MYOMECTOMY LAPAROSCOPIC SURGERY

BUSHRA ABDUL HADI[1]*, SALEH M. SBEITAN[2] and ASHOK K. SHAKYA[1]

[1]Faculty of Pharmacy and Medical Sciences, Al-Ahliyya Amman University-Amman-19328, Jordan
[2]ICU, Specialty Hospital, Amman, Jordan

Abstract: This study was performed to evaluate the efficacy of dexmedetomidine on postoperative pain, analgesics consumption, time for first request of analgesia and the hemodynamic stability 24 h after laparoscopic myomectomy surgery. Sixty patients undergoing double-blind placebo-controlled myomectomy laparoscopic surgery were assigned randomly to 2 groups to be administered either dexmedetomidine as a loading of 1 μg/kg for 10 min followed by a maintenance infusion of 0.5 μg/kg/h (DEX group, n = 30), or a normal saline infusion (CTRL group, n = 30). In a 24 h recovery period, in a post anesthesia care unit (PACU) the first pain score, analgesic requirements, total operation time and the hemodynamic control were measured and observed. Postoperative pain scores and analgesics intake were significantly higher in the normal saline CTRL group comparing to DEX group ($p < 0.05$). Time needed for first request of analgesia was significantly shorter in the normal saline CTRL group comparing to dexmedetomidine DEX group ($p < 0.05$), while the hemodynamic measurements were satisfactory and normal in both groups**.** Intra-operative dexmedetomidine infusion reduces postoperative pain in the first 24 h for patients undergoing myomectomy laparoscopy while providing an ideal hemodynamic stability. Dexmedetomidine could be an adjunct therapy to reduce the postoperative analgesics consumption during myomectomy surgery.

Keywords: dexmedetomidine, myomectomy laparoscopy, postoperative pain, hemodynamic stability

Postoperative pain and hemodynamic stability are the most common therapeutic problems in hospitals (1-3). Various drugs, including ketamine, tramadol, bupivacaine, and lornoxicam have all been reported to be effective adjunct therapy in suppressing postoperative pain (4, 5), in order to reduce morphine consumption. Although many drugs are used to treat postoperative pain, the search for an ideal drug is still ongoing.

α_2-Adrenoceptor agonists are increasingly being used in anesthesia and critical care, as they decrease sympathetic tone and attenuate the stress responses to anesthesia and surgery, in addition to providing sedation and analgesia. Dexmedetomidine is a highly specific α_2-adrenergic receptor agonist. In addition to its sedative features, it increases respiratory stability, decreases opioid need, provides analgesia, helps with early postoperative recovery, and maintains hemodynamics by blocking sympathetic over activity (6-9).

In this double-blind placebo-controlled trial, sixty patients undergoing myomectomy laparoscopic surgery were randomly assigned to either dexmedetomidine treatment group (DEX group) or normal saline group (CTRL group). In addition, information about pain score in laparoscopic *versus* open myomectomy was significant lower after 48 and 72 h (10), and up to best of our knowledge no studies have shown a significant reduction in pain score in the first 24 h in laparoscopic myomectomy.

The primary endpoint is to study the dexmedetomidine efficacy 24 h post-operatively on opioid consumption and time for first request of analgesia. The secondary endpoint of this study was to investigate the cumulative analgesics consumption after surgery, the total duration of surgery and the severity of postoperative pain (as measured using visual analog scale).

EXPERIMENTAL

Materials and methods

This prospective, randomized, double-blind, placebo controlled study was approved by the local

* Corresponding author: e-mail: bushra_abdul@yahoo.com; b.abdelhadi@ammanu.edu.jo

ethics committee. All patients were informed about the details of the procedures and written consent was obtained from each patient. Sixty patients with American Society of Anesthesiologists (ASA) physical status I or II, between the ages of 20 to 45 years and undergoing elective myomectomy laparoscopy, were included in the study. These patients were randomly divided into two groups of 30 patients per group disregarding age and gender. Infertility and pregnancy loss, pelvic pain, and enlarging fibroids (> 2 cm change over 6 months) were the different indications for myomectomy. Both the surgeon and the nursing staff were blind to the analgesic protocol. The same surgeons performed all the operations, and the same nursing staff was responsible for recording the pain scores. The clinical pharmacist and the anesthesiologists, had prepared the study protocol, they were aware of the medications, and observed the patients to avoid or control any adverse drug reaction.

Patients who developed bleeding or hyper-sensitivity to any medication were planned to be excluded from the final study. None of the patients were pre-medicated. In both groups, general anesthesia was induced with i.v. bolus propofol 2.5 mg/kg and fentanyl 1 μg/kg, followed by the administration of rocuronium (0.6 mg/kg) to facilitate endotracheal intubation. General anesthesia was then maintained with sevoflurane (2 ± 0.5% end-tidal oxygen) in a 50% air–oxygen mixture. Ventilation was mechanically controlled to maintain an end-tidal carbon dioxide pressure tension of 30–35 mmHg.

Participants were randomized into 1 of 2 study groups, using a computer-generated random number table, as DEX group and CTRL group. After endotracheal intubation, DEX group received a loading dose of dexmedetomidine of 1 μg/kg over 10 min, followed by an infusion of 0.5 μg/kg/h. CTRL group received 0.9% saline infusion. The drugs were prepared in coded syringes by an anesthesiologist. The infusions were stopped at the end of the operation, and then 1 g of paracetamol was administered by i.v. infusion to all patients. The patients were observed during whole procedure.

Heart rate (HR, beats/min) and mean arterial pressure (MAP, mmHg) hemodynamic parameters were recorded for all patients; before (baseline), and after the operation. Hemodynamic data were recorded postoperatively every 30 min for the first 2 h and then every 4 h till the end of the first 22 h. The total duration of surgery (open to close incision) and the total duration of anesthesia (induction to full recovery) were recorded. At the end of surgery, residual neuromuscular blockade was antagonized with i.v. neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg); where the second drug was given to reverse the para-sympathomimetic effect of neostigmine, both administered together in a single bolus dose from one syringe, and the patients were extubated. In the recovery room, all patients received 50% air–oxygen mixture *via* a face mask and were covered with a cotton blanket and monitored. The postoperative pain was assessed by nurses in charge of the post-anesthesia care unit (PACU) who were not aware of the administered drug.

In the recovery room the assessment of patients' pain scores were done using a visual analog scale (1) at 30 min, 6, 12, and 24 h. Postoperative pain was graded with 0 = no pain, 10 = very severe pain. The patients who had a pain score greater than 4 mm at any time, received 1 mg/kg body weight of intravenous pethidine.

Statistical analysis

To detect a reduction in visual pain score of 0.93, which is in agreement with several studies, with a two-sided 5% significance level and a power of 80%, a sample size of 30 patients per group (60 total) was necessary, given an anticipated dropout rate of 5% (4). All statistical analyses were performed using SPSS (version 17).

The data were expressed as the mean ± SD or median [interquartile range] (range) and were com-

Table 1. Age, body weight, and hemodynamic measurements in the two groups before the operation.

Variable	Group DEX (n = 30)	Group CTRL (n = 30)
Age [a](years)	32.4 ± 5.4	34.3 ± 5.1
Body weight [a](kg)	62.4 ± 9.9	63.9 ± 8.7
Heart rate baseline [b](beats/min)	85 [78-92]	83 [77-90]
MAP baseline [b](mmHg)	80 [73-87]	83 [77-90]

[a]Data are expressed as the mean ± S.D; [b]median [interquartile range].

Table 2. Hemodynamic measurements, the time (min) for the first request for analgesia in the PACU, and the VAS score assessments after 24 h.

Parameters	DEX Group (n = 30)	CTRL Group (n = 30)	p value
Heart rate (beats/ min) (after 22 h)	88 [81-95][a]	90 [82-98][a]	-
MAP (mmHg) (after 22 h)	78 [71-85][a]	81 [73-89][a]	-
Duration of surgery (min)	79.5 [67.5-94.5] (53.0-127.0)	79.5 [67.5-96.0](50.0-126.0)	0.906[#]
Duration of anesthesia (min)	87.0 [71.3-101.8] (62-137)	76.5 [66.0-99.3](59.0-135.0)	0.203[#]
VAS (at 24 h after surgery)	2.0 [1.0-3.0] (1.0-3.0)[b]	3.0 [2.0-4.0] (1.0-5.0)[b]	0.001*
Time for first request of analgesia in PACU (min)	35.9 [34.2-40.0] (34.2-41.2)[b]	12.9 [7.5-14.5] (4.8-16.0)[b]	0.001*

[a]Data are expressed as the median [interquartile range]; [b]median [interquartile range] (range), [c](number of patient and %), *statistically significant difference and [#] statistically no significant difference.

Table 3. Post-operative narcotic analgesic (pethidine) requirement in myomectomy laparoscopic surgery patients.

Time (h)	Test Group (DEX, n = 30),		Control Group (CTRL, n = 30)		p value
	Requirement of pethidine (mg/kg b.w.)[a]	Number and percent of patient requires pethidine	Requirement of pethidine (mg/kg b.w.)[a]	Number and percent of patient requires pethidine	
0	66.0 [62.0-67.0] (60.0-70.0)	(5, 16.7)	63.0 [62.0-69.0] (58.0-72.0)	(17, 56.8)	0.0013*
6	66.0 [64.0-68.0] (62.0-70.0)	(3, 10.0)	65.5 [62.0-70.8] (58.0-72.0)	(10, 33.3)	0.028*
12	66.0 [64.0-68.0] (62.0-70.0)	(2, 6.7)	62.0 [60.5-63.5] (60.0-66.0)	(6, 20.0)	0.129[#]

[a]median [interquartile range] (range), *statistically significant difference, [#]statistically no significant difference (χ^2 test).

pared using Mann-Whitney U test. A p value less than 0.05 was considered statistically significant. Categorical data were described by absolute and percentage frequencies and were compared using χ^2 test. Differences were considered significant when $p < 0.05$.

RESULTS

Patient characteristics were similar in both groups (Table 1). After the pre-operative tests, patients were free of any systemic disease, none of the patients developed bleeding or hyper-sensitivity or any adverse drug reactions to any medication, and they were fit to be operated upon according to the criteria used in this study. No patients were excluded from the study due to any problem mentioned above.

Post-surgical analysis

The hemodynamic measurements (HR, MAP) were stable and within the normal range in both groups and the differences were not significant (Table 2). The total duration of surgery and anesthesia was longer in DEX group but with no significant difference between the two groups. The visual analog scale (VAS) was significantly ($p < 0.001$) lower for DEX group comparing to CTRL group (Fig. 1A and Table 2). Time needed for first request of analgesia was significantly ($p < 0.001$) shorter in CTRL group than DEX group (Fig. 1B-D and Table 2). Table 3 indicates that the requirement of narcotic analgesic (pethidine) was significantly ($p < 0.05$) lower in the patients of treatment group (who have received dexmedetomidine infusion during surgery) than the control group.

In summary, five patients out of 30, of DEX group (~16.7%,) requires pethidine, while 17 patients (56.7%) of CTRL group required pethidine initially (at 0 h, $p < 0.0013$); 33.3% patients of CTRL group required another dose of pethidine to control the pain score (below 4) compared to 10% patients of DEX group ($p < 0.0282$). Results also indicate that the consumption of pethidine in the treatment group was significantly lower than in the control group. This study suggests that the use of dexmedetomidine infusion significantly controls the postoperative pain in first 24 h after surgery.

DISCUSSION

Post-operative analysis

Dexmedetomidine is a pharmacologically active dextrorotatory isomer of medetomidine that displays specific and selective α_2-adrenoceptor ago-

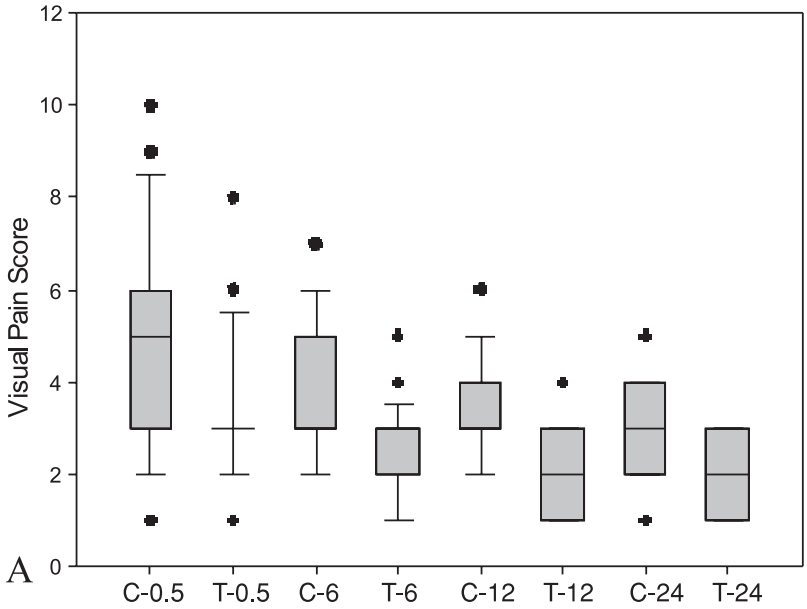

Figure 1A. Time course of the main outcomes registered during the study, that is, the VAS score (C, control; T, Treated patients at time 0.5, 6, 12, and 24 h post-surgery); the pain score on a numerical rating scale from 0 to 10. For each outcome, the diagrams display the median value, the first and third quartile, and the extreme values (crosses) at each period of measurement. The 5 points of measurement were after 0.5, 6, 12 and 24 h after surgery during the stay in post-anesthesia care unit. Patients were discharged after 24 h, unless otherwise mentioned

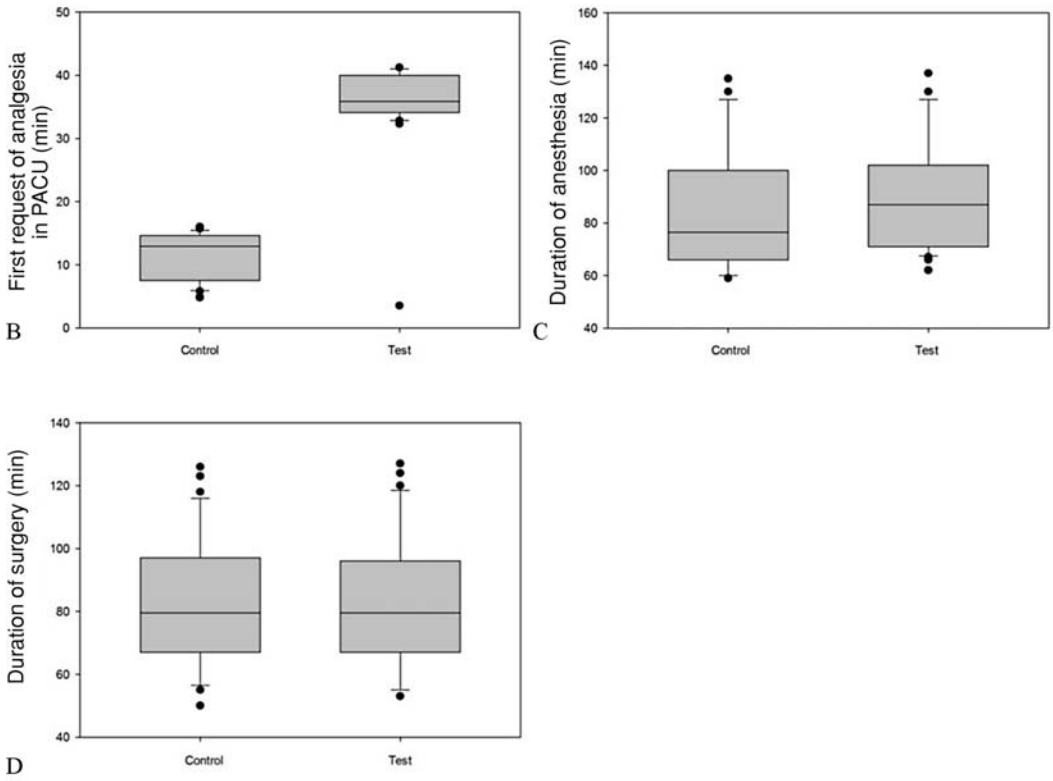

Figure 1B. First request of anesthesia (min) during the stay in PACU ($p = 0.001$), showing significant difference. C. duration of anesthesia ($p = 0.203$. D. duration of surgery ($p = 0.906$) applied to different patients, showing no statistical difference between groups

nism (11). Activation of the receptors in the brain and spinal cord inhibits neuronal firing causing hypotension, bradycardia, sedation, and analgesia (12). In general, pre synaptic activation of the α_2-adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals (13). Postsynaptic activation of α_2-adrenoceptors in the central nervous system inhibits sympathetic activity and thus may lower heart rate and blood pressure (14). It was reported that dexmedetomidine had anesthetic and analgesic effects in addition to its sedative effects (15).

Dexmedetomidine effectively attenuated sympatho-adrenal stimulation during tracheal intubation but did not stop completely the cardiovascular response (16). A need for seeking alternative methods for analgesia occurred since fentanyl was found to have ventilator depressive effect and to cause postoperative nausea and vomiting.

Our results in the present double blind randomized study were similar to these of Feld et al. (17), who studied various alternative methods for analgesia in bariatric surgery. In their study, they compared dexmedetomidine to fentanyl and reported that dexmedetomidine provided stable perioperative hemodynamic and less postoperative analgesia, thus reducing the use of morphine derivatives in the postoperative period. Furthermore, (18) the meta-analysis have confirmed the same. Opioid requirements in the intraoperative period and in the PACU are decreased by dexmedetomidine (16).

In our study, we observed a significant decrease in consumption of analgesics agents post-operatively. Opioid total requirements in the intraoperative period and in the PACU are decreased by dexmedetomidine and clonidine (16, 19). In our study, we observed a significant decrease in consumption of analgesics in the DEX group. On the other hand, patients of normal saline (CTRL) group, required supplemental analgesia earlier than the patients of dexmedetomidine group (DEX group) within the first 24 h (20).

Nakagawa et al. (21) suggested that α_2-adrenergic mechanism of action is involved in the modulation of nociception at the level of spinal noradrenergic systems. There is evidence that α_2-adrenoceptors are located on the dorsal horn neurons of the spinal cord and may release endogenous opiate compounds. Thus, the α_2-adrenoceptor agonists may offer interesting new possibilities in the treatment of pain and may help to decrease intraoperative opioid requirements, similar to clonidine (22, 23). Earlier studies (24, 25) confirmed that application of clonidine relieves hyperalgesia.

In myomectomy surgery, to the best of our knowledge, previous studies did not indicate any significant difference in postoperative pain and consumption of analgesics between the laparoscopic myomectomy or open myomectomy group before the first 72 h observational period. Holzer et al. (10) reported less post analgesics requirements in laparoscopic myomectomy group than the open myomectomy group after 48 and 72 h. Our results are different than the reported results, as the number of patients of DEX group requires less pethidine than number of patient in the CTRL group. In the present research, we documented for the first time a significant difference in pain within 24 h post-myomectomy. Previous studies have shown positive impact of the clinical pharmacists on the surgery. This research was carried out with clinical pharmacist collaborative pivotal pharmacological, and pharmacokinetics knowledge which was provided and discussed with the anesthesiologists in regarding to the major hypothesis of the research, to be in line with the requirements of the times within the operations (2-4, 26).

CONCLUSION

Overall, giving dexmedetomidine in myomectomy showed innovative outcome with less VAS and lower doses of analgesics used within the first 24 h after surgery.We highly recommend using dexmedetomidine in myomectomy surgery as an adjunct therapy for pain management. Collaborative clinical pharmacy practice in the surgery had an effective role to be in line with the requirements of the times within the operations.

Acknowledgments

The authors would like to express their appreciation for the president (Prof. Dr. Sadeq Hamed) and the dean of faculty of pharmacy (Dr. Ghlaeb Orayqat) of Al- Ahliyyaa Amman University for their precious support and assistance during the research procedure.

REFERENCES

1. Hadi B.A., Al-Ramadani R., Daas R., Naylor I., Zelkó R.: Int. J. Clin. Pharmacol. Ther. 48, 542 (2010).
2. Hadi B.A., Al-Ramadani R., Daas R., Naylor I., Zelko R., Saleh M.: South Afr. J. Anaesth. Analg. 15, 10 (2009).
3. Hadi B.A., Daas R., Zelko R.: Saudi. Pharm. J. 21, 169 (2013).

4. Hadi B.A., Sbeitan S.M.: Int. J. Clin. Pharm. 37, 133 (2015).
5. Erdoan I., Çakan T., Özcan A., Türkyilmaz E., Baltaci B., Dikmen B.: AGRI 20, 26 (2008).
6. Belleville J.P., Ward D.S., Bloor B.C., Maze M.: Anesthesiology 77, 1125 (1992).
7. Aho M.S., Erkola O.A., Scheinin H., Lehtinen A.M., Korttila K.T.: Anesth. Analg. 73, 112 (1991).
8. Bloor B.C., Ward D.S., Belleville J.P., Maze M.: Anesthesiology 77, 1134 (1992).
9. Jaakola M.L., Salonen M., Lehtinen R., Scheinin H.: Pain 46, 281 (1991).
10. Holzer A., Jirecek S.T., Illievich U.M., Huber J., Wenzl R.J.: Anesth. Analg. 102, 1480 (2006).
11. McCallum J.B., Boban N., Hogan Q., Schmeling W.T., Kampine J.P., Bosnjak Z.J.: Anesth. Analg. 87, 503 (1998).
12. Sakaguchi Y., Takahashi S.: Masui 55, 856 (2006).
13. Li X., Eisenach J.C.: J. Pharmacol. Exp. Ther. 299, 939 (2001).
14. Ozkose Z., Demir F.S., Pampal K., Yardim S.: J. Exp. Med. 210, 153 (2006).
15. Weinbroum A.A., Ben-Abraham R.: Eur. J. Surg. 167, 563 (2001).
16. Scheinin B., Lindgren L., Randell T., Scheinin H., Scheinin M.: Br. J. Anaesth. 68, 126 (1992).
17. Feld J.M., Hoffman W.E., Stechert M.M., Hoffman I.W., Ananda R.C.: J. Clin. Anesth. 18, 24 (2006).
18. Schnabel A., Meyer-Frießem C.H., Reichl S.U., Zahn P.K., Pogatzki-Zahn E.M.: Pain 154, 1140 (2013).
19. Ghignone M., Quintin L., Duke P.C., Kehler C.H., Calvillo O.: Anesthesiology 64, 36 (1986).
20. Elvan E.G., Oç B., Uzun S., Karabulut E., Coskun F., Aypar U.: Eur. J. Anaesthesiol. 25, 357 (2008).
21. Nakagawa I., Omote K., Kitahata L.M., Collins J.G., Murata K.: Anesthesiology 73, 474 (1990).
22. Tamsen A., Gordh T.: Lancet 2, 231 (1984).
23. Xu M., Kontinen V.K., Kalso E.: Anesthesiology 93, 473 (2000).
24. Davis K.D., Treede R.D., Raja S.N., Meyer R.A., Campbell J.N.: Pain 47, 309 (1991).
25. Sluka K.A., Chandran P.: Pain 100, 183 (2002).
26. Gordon P.C.: South Afr. J. Anaesth. Analg. 10, 7 (2004).

Received: 5. 10. 2016