ORIGINAL ARTICLE

Low-dose spinal neostigmine further enhances the analgesic effect of spinal bupivacaine combined with epidural dexamethasone, following orthopedic surgery

Gabriela Rocha Lauretti, Fabricio S. Veloso, Antonio T Kitayama, Anita Leocadia Mattos[1]
Department of Biomechanics, Medicine and Rehabilitation of Locomotor Members, Discipline of Anesthesia and Pain Management, and [1]Anesthesia, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Background: Opioids are considered mainstream for combined spinal-epidural anesthesia, but frequently limited by adverse effects. The aim of this study was to examine whether low-dose spinal neostigmine, epidural dexamethasone or their combination enhances analgesia from spinal bupivacaine without adverse effects. **Materials and Methods**: A total of 60 patients undergoing orthopedic surgery were randomized to one of four groups and evaluated for 24-h after surgery for analgesia (time to first rescue analgesic) and rescue analgesic consumption. Patients received 15 mg bupivacaine plus the test drug intrathecally (saline or 1 microgram (μg) neostigmine). The epidural test drug was either saline or 10 mg dexamethasone. The Control group (CG) received spinal and epidural saline. The Neostigmine group (NG), spinal neostigmine and epidural saline; the Dexamethasone group (DG), spinal saline and epidural dexamethasone; and the Neostigmine-dexamethasone group (NDG), spinal neostigmine and epidural dexamethasone. **Results:** The CG (282 ± 163 min) and NG (524 ± 142 min) were similar in their times to first rescue analgesic and analgesic consumption. The time to first rescue analgesic was longer for the DG (966 ± 397 min) compared with CG and NG ($P < 0.0002$), and the DG had less ketoprofen consumption and lower overall visual analogue scale-pain sores compared with CG and NG ($P < 0.0005$). Addition of 1 mg-neostigmine (NDG) resulted in longer time to rescue analgesic (1205 ± 303 min; $P < 0.02$) and lower ketoprofen consumption ($P < 0.05$) compared to DG. Sporadic cases of vesical catheterization and emesis were observed, however adverse effects were similar among groups. **Conclusion:** Spinal 1 microgram (μg) neostigmine further enhanced analgesia from spinal bupivacaine combined with epidural dexamethasone, without increasing the incidence of adverse effects.

Key words: Epidural dexamethasone, postoperative analgesia, spinal neostigmine

How to cite this article: Lauretti GR, Veloso FS, Kitayama AT, Mattos AL. Low-dose spinal neostigmine further enhances the analgesic effect of spinal bupivacaine combined with epidural dexamethasone, following orthopedic surgery. J Res Med Sci 2014;19:801-6.

INTRODUCTION

Efforts to improve combined spinal-epidural (CSE) technique have focused on adding opioids to other classes of analgesics, exemplifying multimodal analgesia.[1-3] Opioids are considered excellent analgesics, but their clinical effectiveness is frequently limited by adverse effects.[4,5] By contrast, nonnarcotic agents may represent the ideal approach for outpatients undergoing minor orthopedic procedures, and there are encouraging trials of nonopioid drugs in CSE technique.[6,7] Among nonnarcotics, neostigmine was suggested to be more efficacious for somatic then for visceral pain,[8] making it attractive for orthopedic procedures.

On the other hand, epidural dexamethasone has been extensively evaluated for visceral[9,10] and neuropathic[11,12] types of pain, but not for the somatic pain, such as orthopedic procedures, to our knowledge. Because steroids such as dexamethasone are known to share certain mechanisms of action with nonsteroidal antiinflammatory drugs (NSAID),[13] and since the co-administration of neostigmine with NSAID resulted in a synergistic interaction in mice,[14] the purpose of this study was to determine whether the combination of either low-dose intrathecal neostigmine or epidural dexamethasone, or both, enhances analgesia from spinal bupivacaine in minor orthopedic surgery, an example of somatic pain, once in spite of evaluation in animals, this association has not been evaluated in patients to date.

MATERIALS AND METHODS

The Local Ethical Committee of the Teaching Hospital of the School of Medicine of Ribeirão Preto from the University of São Paulo, Brazil, approved this protocol (Governmental Clinical Trial HC-7189-2008). After

Address for correspondence: Prof. Gabriela Rocha Lauretti, Rua-Maestro Joaquim Rangel, 644, Ribeirão Preto, São Paulo - 14025-610, Brazil.
E-mail: grlauret@fmrp.usp.br
Received: 25-10-2013; **Revised:** 27-11-2013; **Accepted:** 01-06-2014

gaining the subjects approval and written informed consent, 60 American Society of Anesthesiology (ASA) Status I and II patients, 18-60 year old, undergoing minor orthopedic surgery were computer randomized to one of four groups (n = 15) and prospectively evaluated using a placebo-controlled double-blind design to examine both analgesia and perioperative adverse effects. The concept of a visual analog scale (VAS),[15] which consisted of a 10 cm line with 0 equaling "no nausea" (VAS N) or "no pain at all" and 10 equaling "worst possible nausea" or "the worst possible pain" was introduced to the subjects before surgery. Exclusion criteria included diabetes, glaucoma, patient´s refusal or allergy for any of the study drugs.

The patients were premedicated with 0.05-0.1 μg/kg intravenous (IV) midazolam immediately before going to the operating room. Hydration consisted of a rapid infusion of 10 ml/kg lactate solution before surgery and 10 ml/kg/h after intrathecal anesthesia. CSE anesthesia was performed in theater at the L2-L3 (epidural) and L3-L4 (spinal) interspaces in the sitting position. One anesthesiologist prepared the test drugs, while a different one performed the spinal/epidural punctures. The epidural test drug was either saline or 10 mg dexamethasone diluted in saline (for a final volume of 10 ml) injected as a bolus. Just after epidural drugs administration, spinal drugs were injected at 1 ml per 7 s through a 25-gauge intrathecal needle. All patients received 15 mg bupivacaine plus 1 ml of saline or 1 μg neostigmine [Table 1].[16] Patients from the Control group (CG) received spinal saline and epidural saline as the test drugs. Patients from the Neostigmine group (NG) received spinal neostigmine and epidural saline. Patients from the Dexamethasone group (DG) received spinal saline and epidural dexamethasone, and patients from the Neostigmine-dexamethasone group (NDG) received spinal neostigmine and epidural dexamethasone. Patients were placed supine immediately after the spinal/epidural punctures. Further IV midazolam was given according to the anesthesiologist's judgment.

Table 1: Experimental groups

Groups	Intrathecal drugs (final volume 4 ml)	Epidural drugs (final volume 10 ml)
CG	Hyperbaric 0.5% bupivacaine (15 mg, 3 ml)+1 ml saline	Saline (10 ml)
NG	Hyperbaric 0.5% bupivacaine (15 mg, 3 ml)+1 microgram (μg) neostigmine (1 ml)	Saline (10 ml)
DG	Hyperbaric 0.5% bupivacaine (15 mg, 3 ml)+1 ml saline	10 mg depo-dexamethasone (2 ml)+saline (8 ml)
NDG	Hyperbaric 0.5% bupivacaine (15 mg, 3 ml)+1 microgram (μg) neostigmine (1 ml)	10 mg depo-dexamethasone (2 ml)+saline (8 ml)

CG = Control group; NG = Neostigmine group; DG = Dexamethasone group; NDG = Neostigmine-dexamethasone group

The quality of sensation of the anaesthetized areas as described by the patient during the blockade installation was recorded as either:

1. Heaviness;
2. Increase in temperature;
3. Numbness or
4. Pricking. Intraoperative sensory loss assessment included the pinprick test at 5 and 10 min after the spinal anesthesia.

Blood pressure was monitored noninvasively every 5 min throughout surgery, and heart rate and oxyhemoglobin saturation (SpO_2) were continuously monitored throughout surgery. A decrease in mean arterial pressure >15% below preanesthetic baseline was treated with incremental doses of ephedrine. Decreases in heart rate below 50 bpm were treated with atropine, 0.25 mg IV, according to the anesthesiologist's judgment. Intraoperative nausea was scored by the patient using the 10 cm VAS N. The numbers of patients with nausea (of any degree) or vomiting at any time intraoperatively were noted. Nausea >2/10 at any time or vomiting during the study was treated with 8 mg IV ondansetron, if necessary. For patients with >1 episode of nausea, the VAS scores were averaged.

Postoperative assessment included pain scores, adverse effects and the duration of motor block, measured from spinal anesthesia until time to reach a Bromage 2 score. Patients were free to receive rescue analgesics at the time requested. IV ketoprofen 50 mg was available at 4-h-intervals. The second rescue analgesic drug was the nonsteroidal dipyrone (1 g), administered intravenously, 1-h after the ketoprofen, if necessary, at 6-h-intervals. Pain was assessed at the time of the first rescue analgesic and 24-h after the spinal puncture by the anesthesiologist who was blind to the treatment. Nausea and occurrence of vomiting were assessed intraoperatively and 24-h after the spinal puncture by the same anesthesiologist, blind to the treatment. The duration of efficacious analgesia was measured as the time from the spinal anesthesia to the patient's first request for analgesics either in the recovery room or infirmary, recorded in min. The VAS at the time of the first rescue analgesic was measured using the 10 cm VAS. The 24-h VAS pain score and VAS N reflected the patient's overall impression of the 24-h following spinal injection.

Statistical analysis

The power of the study was based upon preliminary data. We hypothesized that 10 mg of epidural dexamethasone would increase the time to first rescue analgesic by 100% compared to the CG in the population studied, and expected that the addition of intrathecal neostigmine would further increase the time to first rescue analgesic by 20% compared to the DG. If a standard deviation was estimated, an 80%

and an alpha value of 0.05, these assumptions would require 12 patients in each group.

The normality of the distributions was assessed using the Shapiro–Wilk's test. Groups were compared for demographic data (i.e., age, weight and height) and duration of surgery by one-way ANOVA. Incidence of adverse events, gender, ASA status and adjuvant drug use were compared among groups by Chi-square corrected for multiple comparisons. $P < 0.0125$ was considered as significant (i.e., 0.05 divided by the number of groups). Blood pressure, heart rate, level of anesthesia (by pinprick test) and VAS scores were compared among groups by two-way ANOVA for repeated measures. Tukey analysis was applied to decrease the probability of type I error. The time to first rescue analgesics and the analgesic consumption (mg) in 24-h were compared using the Kruskal–Wallis on ranks followed by the Student-Newmans-Keuls test. $P < 0.05$ was considered significant. Data are expressed as means ± SD, unless otherwise stated.

RESULTS

A total of 57 patients were evaluated [Figure 1]. 1 patient from the NG was excluded from the study due to incomplete data collection, while 2 patients from the CG declined to participate. All patients underwent minor orthopedic surgeries. 6 patients in the CG, NG and NDG; and 7 patients in the DG underwent knee arthroscopy/meniscus repair, while the others underwent knee ligamental reconstruction ($P > 0.05$). The four groups showed no differences regarding ASA status, gender, age, weight or height [$P > 0.05$, Table 2]. The numbers of patients in each group reporting either:

1. Heaviness;
2. Increase in temperature;
3. Numbness or
4. A prickly sensation, as the main sensation in the anaesthetized area during the blockade installation are described in Table 3 ($P > 0.05$).

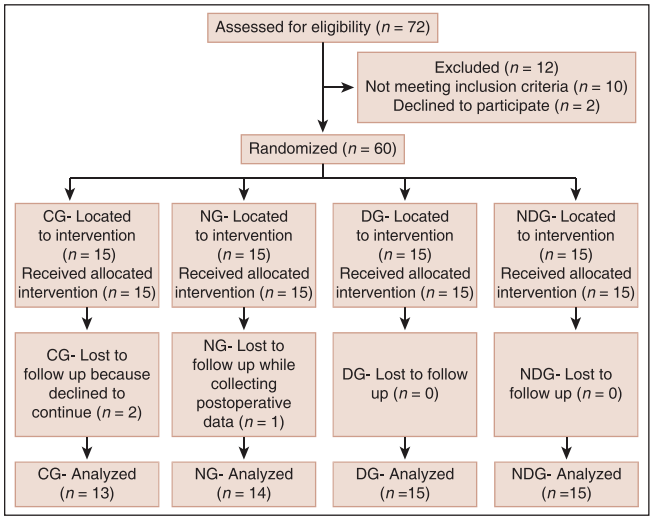

Figure 1: Flow diagram of progress through the phases enrolment, allocation, follow-up and analysis

The sensory level to pinprick at 5 and 10 min after the spinal puncture, surgical and anesthetic time, and intraoperative ephedrine consumption were similar among the groups [Table 4]. The intraoperative hemodynamic data in different time intervals in four groups was similar ($P > 0.05$, data not shown). The intraoperative midazolam administration was also similar among the groups (2-4 mg, $P > 0.05$).

The postoperative data are presented in Table 5. The pain VAS score at the time of the first rescue analgesic medication was similar among the four groups ($P > 0.05$). The CG was similar to the NG related in time to first rescue analgesic, IV ketoprofen consumption and overall VAS–pain impression. The time to first rescue analgesic was longer for the DG compared to both the CG and NG ($P < 0.0002$), and the DG had less ketoprofen consumption and lower overall VAS-pain sores compared to both CG and NG ($P < 0.0005$). The addition of 1 μg neostigmine (NDG) resulted in a longer time to rescue analgesic ($P < 0.02$) and lower ketoprofen

Table 2: Demographic data

Groups	ASA (I/II)	Gender (male/female)	Weight (kg)*	Age (years)*	Height (cm)*
CG	9/4	8/5	73±11	36±8	172±6
NG	10/4	10/4	78±14	33±8	173±9
DG	11/4	9/6	72±14	35±11	171±10
NDG	10/5	12/3	74±14	33±10	173±11

$P > 0.05$. *Data expressed as mean ± SD. ASA = American Society of Anesthesiology; CG = Control group; NG = Neostigmine group; DG = Dexamethasone group; NDG=Neostigmine-dexamethasone group; SD = Standard deviation

Table 3: Quality of sensation described by the patient during the spinal/epidural blockade installation

Groups	CG	NG	DG	NDG
Increase in temperature	8	9	11	10
Pricking	4	4	2	3
Heaviness	0	0	0	0
Numbness	1	1	2	2

Data presented as number of patients describing anesthesia characteristics. $P > 0.05$. CG = Control group; NG = Neostigmine group; DG = Dexamethasone group; NDG = Neostigmine-dexamethasone group

Table 4: Characteristics of the spinal block

Groups	CG	NG	DG	NDG	*P* value
Pinprick (5 min)*	11 (10-12)	11 (11-12)	11 (11-12)	11 (10-11)	*P*>0.05
Pinprick (10 min)**	10 (10-11)	9 (9-10)	9 (9-10)	9 (9-10)	*P*>0.05
Surgical time (min)	110±28	112±39	119±33	116±34	*P*>0.05
Partial motor block (min)**	170±23	213±15	210±20	212±19	*P*>0.05

**$P < 0.05$: CG compared to the others. Pinprick refers to dermatome anesthesia to a pinprick on the skin. Partial motor block refers to time from spinal injection to reach Bromage score 2. *Median (25%-75% percentile confidence). Other data expressed as mean ± SD. CG = Control group; NG = Neostigmine group; DG = Dexamethasone group; NDG = Neostigmine-dexamethasone group; SD = Standard deviation

Table 5: Postoperative analgesia data

Groups	Time to first rescue analgesic (min)*	VAS at first rescue analgesic (cm)	IV ketoprofen consumption in 24-h (mg)**	Overall 24-h VAS pain (cm)#
CG	282±163	6.9±1.3	177±40	3.3±1.7
NG	524±142	6.3±1.3	114±46	2.7±0.9
DG	966±397	6.5±1.1	44±36	1±1.6
NDG	1205±303	6.4±0.6	17±24	0.6±1
P	<0.02	>0.05	<0.05	<0.05

*CG < other groups ($P < 0.02$), NG < DG ($P < 0.0002$), NG < NDG ($P < 0.0002$), NDG > DG ($P < 0.02$); **CG = NG ($P > 0.05$), CG = NG > DG ($P < 0.0002$), CG = NG > NDG ($P < 0.0002$), NDG > DG ($P < 0.05$); #CG = NG ($P > 0.05$), DG = NDG ($P > 0.05$), CG = NG > DG ($P < 0.0005$), CG = NG > NDG ($P = 0.0002$). Data expressed as mean ± SD. VAS = Visual analog scale; IV = Intravenous; CG = Control group; NG = Neostigmine group; DG = Dexamethasone group; NDG=Neostigmine-dexamethasone group; SD = Standard deviation

consumption ($P < 0.05$) compared to the DG. 5 patients in the DG and 9 patients in the NDG did not request any analgesic during the 24-h evaluation. All other patients requested a rescue analgesic at least once; however, no patients needed dipyrone.

There were no differences in the incidence of perioperative adverse effects ($P > 0.05$). Intraoperatively, only 1 patient from the NG complained of transient intraoperative nausea (VAS 3 cm); however, and no pharmacological treatment was necessary ($P > 0.05$). Postoperatively, 1 patient from the NG had vomited once after dinner; however, no pharmacological treatment was necessary. 1 patient from the DG complained of nausea (VAS 5 cm) followed by transient headache. This patient preferred only to rest because she had a history of headache. Two patients from the NDG needed vesical catheterization at 6 and 7-h after the spinal puncture. There were no other spontaneous complaints from the patients ($P > 0.05$).

DISCUSSION

Here, we report a significant enhancement of the analgesic effect of spinal bupivacaine plus epidural dexamethasone by a combination with an intrathecal injection of 1 μg of neostigmine in patients that underwent minor orthopedic procedures. This is the third double-blind clinical evaluation demonstrating enhancement of opioid analgesia after such a low-dose of neostigmine,[16,17] and the first clinical trial to demonstrate enrichment from the combination of spinal neostigmine and epidural dexamethasone.

Epidural steroid injections have been used in acute pain under different circumstances, that is, in patients suffering from spinal stenosis,[18] in which exacerbations of a chronic pain state occurs;[19] or for acute postoperative pain, in which epidural 5 mg of dexamethasone, before or after surgery reduces pain and analgesic requirement after radical subtotal gastrectomy.[20] The use of dexamethasone at a dose of 10 mg instead of 5 mg was based on a pilot study, in which 5 mg of epidural dexamethasone produced little analgesic effect in a similar population. In this study, the addition of 10 mg of epidural dexamethasone to spinal bupivacaine resulted in a longer time to first rescue analgesic and less rescue analgesic consumption over 24-h. Moreover, 30% of patients in the DG did not request any rescue analgesic, which was further optimized to 60% by the addition of 1 μg of neostigmine.

Epidural dexamethasone may be acting at spinal sites by inducing the synthesis of the phospholipase-A2 inhibitory protein lipocortin,[21] and thus, reducing prostaglandin and leukotriene synthesis and suppressing hyperalgesia associated with acute nociception during surgery. In addition, high levels of glucocorticoid receptor and mineralocorticoid receptor are colocalized in the substantia gelatinosa,[22] suggesting that the pain pathways are strongly regulated by these receptors. Dexamethasone was also shown to down-regulate cyclooxygenase-2 mRNA, an important step for its antiinflammatory action.[23] Epidural dexamethasone could also cross through the spinal hole from the epidural into the spinal canal and inhibit the induction of excitatory amino acids, important neurotransmitters in central sensitization. Spinal dexamethasone was demonstrated to modulate the development of morphine tolerance and the expression of glutamate transporters in rats.[24]

In this study, 1 μg of spinal neostigmine did not enhance the analgesic effect of spinal bupivacaine, but potentiated the analgesic effect of epidural dexamethasone. One μg spinal neostigmine has been previously demonstrated to enhance intrathecal morphine analgesia following orthopedic surgery combined to intrathecal morphine[16] and to intrathecal fentanyl.[17] The analgesic effect of spinal neostigmine was suggested to result from an increase in the concentration of the neurotransmitter acetylcholine, and its consequent action at muscarinic M1 and M3 and presynaptic nicotinic receptors,[25] present in the cholinergic interneurons at the laminae II and V of the dorsal horn. The inhibitory action at muscarinic receptors of dorsal horn neurons was suggested to be mediated in part by spinal gamma amino butyric acid-B receptors.[26] Intrathecal neostigmine also induced nitric oxide release in the spinal cord, suppressed Fos expression[27] and facilitated the activation of spinal M(2) receptors, ultimately leading to the release of adrenal catecholamines. These mediators which contributed to the antiinflammatory effect observed at the site of tissue inflammation.[28]

In addition to the apparent synergistic interaction between spinal neostigmine/bupivacaine and epidural dexamethasone observed in the present study, an

interaction between ketoprofen, used as first line rescue analgesic, and spinal neostigmine in mice has been described.[14] However, an interaction between ketoprofen and the study drugs can be ruled out, because neither group showed enhanced postoperative analgesia after ketoprofen administration. One explanation for the lack of synergy effect between ketoprofen and neostigmine could be the low-dose used (1 μg) in the NG. Unfortunately, neither intraoperative nor postoperative sedation was evaluated, as epidural dexamethasone could have interfered with it.[29]

CONCLUSION

Spinal 1 μg neostigmine further enhanced analgesia from spinal bupivacaine combined with epidural dexamethasone, without increasing the incidence of adverse effects in the population studied, suggesting a role for a multimodal approach, including these drugs in the management of postoperative analgesia following minor orthopedic surgery.

AUTHORS CONTRIBUTION

GRL-Data compilation, writing the manuscript, statistics.

FSV-Data collection, performing anesthesia,randomization.

AT-Data collection, performing anesthesia.

ALM-Performing anesthesia, writing the manuscript.

REFERENCES

1. Owen MD, Ozsaraç O, Sahin S, Uçkunkaya N, Kaplan N, Magunaci I. Low-dose clonidine and neostigmine prolong the duration of intrathecal bupivacaine-fentanyl for labor analgesia. Anesthesiology 2000;92:361-6.
2. D'Angelo R, Dean LS, Meister GC, Nelson KE. Neostigmine combined with bupivacaine, clonidine, and sufentanil for spinal labor analgesia. Anesth Analg 2001;93:1560-4.
3. Chang FL, Ho ST, Sheen MJ. Efficacy of mirtazapine in preventing intrathecal morphine-induced nausea and vomiting after orthopaedic surgery*. Anaesthesia 2010;65:1206-11.
4. Düger C, Gürsoy S, Karadağ O, Kol IÖ, Kaygusuz K, Özal H, *et al*. Anesthetic and analgesic effects in patients undergoing a lumbar laminectomy of spinal, epidural or a combined spinal-epidural block with the addition of morphine. J Clin Neurosci 2012;19:406-10.
5. Black AS, Newcombe GN, Plummer JL, McLeod DH, Martin DK. Spinal anaesthesia for ambulatory arthroscopic surgery of the knee: A comparison of low-dose prilocaine and fentanyl with bupivacaine and fentanyl. Br J Anaesth 2011;106:183-8.
6. Dobrydnjov I, Axelsson K, Gupta A, Lundin A, Holmström B, Granath B. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: A double-blind, randomized and placebo-controlled study. Acta Anaesthesiol Scand 2005;49:538-45.
7. Arcioni R, Palmisani S, Tigano S, Santorsola C, Sauli V, Romanò S, *et al*. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce post-operative analgesic requirements: A prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery. Acta Anaesthesiol Scand 2007;51:482-9.
8. Lauretti GR, Lima IC. The effects of intrathecal neostigmine on somatic and visceral pain: Improvement by association with a peripheral anticholinergic. Anesth Analg 1996;82:617-20.
9. Khafagy HF, Refaat AI, El-Sabae HH, Youssif MA. Efficacy of epidural dexamethasone versus fentanyl on postoperative analgesia. J Anesth 2010;24:531-6.
10. Kim EM, Lee JR, Koo BN, Im YJ, Oh HJ, Lee JH. Analgesic efficacy of caudal dexamethasone combined with ropivacaine in children undergoing orchiopexy. Br J Anaesth 2014;112:885-91.
11. Kim EJ, Moon JY, Park KS, Yoo da H, Kim YC, Sim WS, *et al*. Epidural steroid injection in korean pain physicians: A national survey. Korean J Pain 2014;27:35-42.
12. Kennedy DJ, Plastaras C, Casey E, Visco CJ, Rittenberg JD, Conrad B, *et al*. Comparative Effectiveness of Lumbar Transforaminal Epidural Steroid Injections with Particulate Versus Nonparticulate Corticosteroids for Lumbar Radicular Pain due to Intervertebral Disc Herniation: A Prospective, Randomized, Double-Blind Trial. Pain Med 2014;15:548-55.
13. Zhu TS, Glaser M. Neuroprotection and enhancement of remyelination by estradiol and dexamethasone in cocultures of rat DRG neurons and Schwann cells. Brain Res 2008;1206:20-32.
14. Miranda HF, Sierralta F, Pinardi G. Neostigmine interactions with non steroidal anti-inflammatory drugs. Br J Pharmacol 2002;135:1591-7.
15. Rauh KH, Andersen RS, Rosenberg J. Visual analogue scale for measuring post-operative pain. Ugeskr Laeger 2013;175:1712-6.
16. Almeida RA, Lauretti GR, Mattos AL. Antinociceptive effect of low-dose intrathecal neostigmine combined with intrathecal morphine following gynecologic surgery. Anesthesiology 2003;98:495-8.
17. Jain A, Jain K, Bhardawaj N. Analgesic efficacy of low-dose intrathecal neostigmine in combination with fentanyl and bupivacaine for total knee replacement surgery. J Anaesthesiol Clin Pharmacol 2012;28:486-90.
18. Friedly JL, Bresnahan BW, Comstock B, Turner JA, Deyo RA, Sullivan SD, *et al*. Study protocol-Lumbar Epidural steroid injections for Spinal Stenosis (LESS): A double-blind randomized controlled trial of epidural steroid injections for lumbar spinal stenosis among older adults. BMC Musculoskelet Disord 2012;13:48.
19. Carragee EJ, Hurwitz EL, Cheng I, Carroll LJ, Nordin M, Guzman J, *et al*. Treatment of neck pain: Injections and surgical interventions: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976) 2008;33:S153-69.
20. Jo YY, Yoo JH, Kim HJ, Kil HK. The effect of epidural administration of dexamethasone on postoperative pain: A randomized controlled study in radical subtotal gastrectomy. Korean J Anesthesiol 2011;61:233-7.
21. Hirata F, Schiffmann E, Venkatasubramanian K, Salomon D, Axelrod J. A phospholipase A2 inhibitory protein in rabbit neutrophils induced by glucocorticoids. Proc Natl Acad Sci U S A 1980;77:2533-6.
22. Gu X, Peng L, Yang D, Ma Q, Zheng Y, Liu C, *et al*. The respective and interaction effects of spinal GRs and MRs on radicular pain induced by chronic compression of the dorsal root ganglion in the rat. Brain Res 2011;1396:88-95.
23. Inoue A, Ikoma K, Morioka N, Kumagai K, Hashimoto T, Hide I, *et al*. Interleukin-1beta induces substance P release from

primary afferent neurons through the cyclooxygenase-2 system. J Neurochem 1999;73:2206-13.
24. Wen ZH, Wu GJ, Chang YC, Wang JJ, Wong CS. Dexamethasone modulates the development of morphine tolerance and expression of glutamate transporters in rats. Neuroscience 2005;133:807-17.
25. Kiyosawa A, Katsurabayashi S, Akaike N, Pang ZP, Akaike N. Nicotine facilitates glycine release in the rat spinal dorsal horn. J Physiol 2001;536:101-10.
26. Chen SR, Pan HL. Activation of muscarinic receptors inhibits spinal dorsal horn projection neurons: Role of GABAB receptors. Neuroscience 2004;125:141-8.
27. Lin X, Wang Q, Huang W, Zhu L, Yang B. Study on the mechanism of antinociception of intrathecal neostigmine in the formalin test in rats. Sichuan Da Xue Xue Bao Yi Xue Ban 2003;34:698-700.
28. Yoon SY, Kwon YB, Kim HW, Roh DH, Kang SY, Kim CY, *et al*. Intrathecal neostigmine reduces the zymosan-induced inflammatory response in a mouse air pouch model via adrenomedullary activity: Involvement of spinal muscarinic type 2 receptors. Neuropharmacology 2005;49:275-82.
29. Lauretti GR, Rizzo CC, Mattos AL, Rodrigues SW. Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone. Br J Cancer 2013;108:259-64.

Source of Support: Nil, **Conflict of Interest:** None declared.