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The Management Of Perioperative Pain Controlling: The Purpose Of Epidural Prostigmin With Paceco Seuss Avenue And Doing Partial Hepatectomy

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Abstract
Patient-controlled epidural analgesia (PCEA) is a common postoperative technique of alleviating pain that is usually a combination of a local anesthetic and an opioid drug. Nonetheless, opioids are connected to dose-based side effects, which include nausea, vomiting, itching, low breathing rate, and urinary retention. The recent literature implies that the use of acetylcholine esterase such as Prostigmin to the epidural inhibits analgesia by utilized in the spinal cord region. This paper sought to establish the most appropriate single dose of epidural Prostigmin when using PCEA so as to get acceptable level of postoperative analgesia after partial hepatectomy. There were 50 patients recruited and the dosage of Prostigmin was given following a fixed schedule of the dose with an epidural system. The post-surgery analgesia quality was evaluated 8 and 24 hours after the surgery with the reference to the variables: the time of the first PCEA bolus administration, VAS scores, boluses usage. The difference in the result was that the Dixon up-and-down method resulted in 50 percent effective dose (ED50) of 228.63 +- 183 mg and 95 percent effective dose (ED95) of 300.12 +- 224 mg epidural Prostigmin. The patients, which belonged to the good analgesia group, received a lower number of PCEA boluses and showed substantially reduced VAS scores, which indicated that epidural Prostigmin, along with PCEA, offers effective and long-lasting pain control and eliminates the use of great amounts of opioids. This paper demonstrates the opportunity of epidural Prostigmin as an encouraging addition in the combination of opioids and local anesthetics to relieve postoperative pain. Future study involving greater sample size and longer follow-up is necessary to find the optimum dose and the long-term efficiency of the approach.
Keywords: Patient-controlled epidural analgesia (PCEA), Epidural Prostigmin, Postoperative analgesia, Partial hepatectomy, Visual analog scale (VAS)

Introduction
One of the most used types of pain relief following a surgical procedure is patient-controlled epidural analgesia (PCEA) comprising both local anesthetics and opioids. Nevertheless, multiple dose-dependent adverse effects are linked with opioids such as nausea, vomiting, itching, respiratory depressions, some urinary retention. Recent research indicates that analgesia can be augmented by adding some acetylcholinesterase inhibitors (e.g.: Prostigmin) into the epidural that acts on the spinal cord. Other studies have shown the effect of adding local anesthetics and epidural Prostigmin to reduce pain scores as in the visual analogue scale

(VAS) but also prolongs the duration of postoperative analgesia when studied in doses of 1 to 10 10uG/kg. No definitive evidence exists however on what the single dose of epidural Prostigmin should be in postoperative pain management. The objective of this research abstract is to define the most effective single dose of epidural Prostigmin, when combined with PCEA, in giving effective post hepatectomy pain reduction.

Patients and Methods

Patients

There were 50 patients who were used in the study to perform elective partial hepatectomy of ages 18-64 years and ASA physical status I-II. The screening rules were the previous or current history of the heart or lung diseases, severe dysfunction of the liver or kidney, disorders during the coagulation of the blood, or the administration of analgesics used to treat chronic pain. All the patients were treated with routine preoperative preparation. Everyone had more than 10 hours of fasting before the surgery, and pre-surgery drugs were not given.

Anesthesia

Majority of patients were given an epidural line on T8 and T9 and 4 ml of 1 % lidocaine injected through it to ascertain proper position. 3 ug/kg fentanyl and target-controlled infusion of propofol (4 ug/kg) delivered were used as general anesthesia, rocuronium (0.6 mg/kg) to intubation of the trachea, and ventilated the ventilator in normocapnia (ETCO2 35-40 mmHg) with the mixture of 50 percent oxygen and air. After induction, 0.5% bupivacaine was used in small doses (8-12 ml) and the anesthesia was kept with additional 3-5 ml of bupivacaine every hour as a bolus during the surgery. Desflurane was used to administer general anesthesia, and targeting concentrations were 4.5-6.0 vol % which were kept under monitoring through hemodynamic parameters. After thirty minutes of incision (skin incision), Prostigmin (diluted with 5 ml normal saline) was administered through the front of the epidural catheter. Extra shots of rocuronium were administered to guarantee that the muscles in the body grew to be relaxed throughout the surgical process. Monitoring the hemodynamic condition was performed with the help of a three-lead electrocardiogram, pulse oxymeter on fingers, and constant catheter of the radial artery with direct measurement of the blood pressure. Phenylephrine was used in case the mean arterial pressure became less than 60 mmHg. The IV fluids that were used were Lactated Ringer and Hydroxyethyl Starch 130/0.4 Sodium Chloride Injection in the ratio of 3:1, and this was infused as per the loss of blood and hemodynamic values. Tropisetron 6 mg was injected half an hour prior to the completion of the procedure. Postoperatively all the patients were administered with PCEA that contained 0.125% bupivacaine and 28g fentanyl with background infusions of 2.5 ml/h with 4 ml bolus and lockout time of 10 minutes.

Experimental Protocol

The first patient was set at 100 5g to start with the epidural Prostigmin dose because the past researches allowed us to use this amount. Depending on the estimated standard deviation of the ED50 it was decided to administer the doses according to a predetermined interval. Quality of analgesia at 8 hours and 24 hours postoperative was determined by the scoring system with the inclusion of the following variables, i.e. duration of analgesia before using the first PCEA bolt,

VAS score, and PCEA boluses used. All of these variables were evaluated and termed as either good or poor. Analgesia was deemed satisfactory when all variables were within acceptable range, and unsatisfactory when any variable was poor. The quality of analgesia was assessed by an experienced anesthesiologist who was unaware of the epidural Prostigmin dose. The ratings of the variables were the basis of defining what is a satisfactory analgesia and what is unsatisfactory analgesia.

Statistical Analysis

The analysis of categorical data, including gender, ASA physical status, was carried by the Chi-squared and Fisher exact tests. Continuous data were given as mean + SD, and independent-samples t-tests were used. The seven pairs of data were obtained by the use of Dixon up and down method whereby an increase in the dose of Prostigmin reversed the response to Prostigmin as being negative to positive. Fifty patients were used in this data collection procedure. The ED50 of epidural Prostigmin was regarded as a half of the calculation of the midpoint drug dose per each independent pair of the crossover points of the seven patients. The probit regression was taken to identify the ED 50, ED 95 and 95 percent confidence interval (CI). The mark produced by the probit analysis was done using SPSS 19.0 windows package and p-value of less than 0.05 was determined as being significant.

Results

The review of the quality of analgesia 24 hours after the operation revealed that patients who had pain well-controlled (n = 30) had a long time, usually more than 8 hours, to the first PCEA bolus, when compared to the poorly-analgesic patients (n = 20), who needed the first bolus was less than 8 hours. The VAS scores of good analgesic patients ranged between 0-3 while poor ones had a high reading (4-10) with respect to the VAS. Moreover, the patients with satisfactory analgesia needed fewer PCEA boluses, with most of them using 0-8 boluses, whereas with poor analgesia patients received more frequent boluses, and more than 8 have been administered within the 24-hour period. These results draw the model that shows a very important difference between well-controlled and poorly managed patients according to the timing of the boluses and discusses the VAS at the top and then the number of boluses to reach an appropriate level of pain control.

Table 1: Evaluation of the Quality of Analgesia 24 Hours After the Operation

Variables	Good (n = 30)	Poor (n = 20)
Time to the first PCEA bolus	> 8 hours	≤ 8 hours
VAS score	0-3	4-10
Number of PCEA boluses	0-8	>8

VAS: visual analog scale, **PCEA:** Patient controlled epidural analgesia,

The nature of patients in terms of their population and operative conditions was compared in the population of patients with satisfactory and dissatisfactory analgesia. The two groups had a comparable average age of patients with the good analgesia group being older (49.50 8.75 years) than the dissatisfactory one (48.90 10.12 years). The gender distribution indicated that a larger number of male patients were in the satisfying analgesia one (22/8) than reported in

the non-satisfying one (14/6). The two groups did not differ in terms of weight, whereby the satisfactory group had an average of 65.30 +/- 9.75 kg and the dissatisfactory group 63.10 +/- 10.12 kg. The two groups also compared in terms of body mass index (BMI) where the value was 23.10 2.45 kg/m 2 in the satisfactory group and 22.50 2.30 kg/m 2 in the dissatisfactory group. In view of the ASA physical status, the number of patients in the satisfactory group (25 patients) was higher as ASA I compared to (14 patients) in the dissatisfactory group, meaning that the proportion of patients who have better health is high in the satisfactory group. The time of surgery did not differ significantly when it comes to the differences between satisfactory analgesia group and dissatisfactory analgesia group 132.5 39.10 minutes versus 135.0 33.80 minutes respectively, which is indicative that the length of surgery was not an important factor in determining the analgesia quality.

Table 2: The demographical statistics together with the nature of the patients, as far as the surgery is concerned is enumerated

Variables	Satisfactory Analgesia (n = 30)	Dissatisfactory Analgesia (n = 20)
Age (years)	49.50 ± 8.75	48.90 ± 10.12
Gender (male/female)	22/8	14/6
Weight (kg)	65.30 ± 9.75	63.10 ± 10.12
Body Mass Index (kg/m²)	23.10 ± 2.45	22.50 ± 2.30
ASA Physical Status (I/II)	25/5	14/6
Duration of Operation (min)	132.5 ± 39.10	135.0 ± 33.80

ASA= American Society of anesthesiologists

The PCEA data at 24 hours post elective partial hepatectomy was found to be highly different between two groups. The mean time to when the first PCEA bolus was administered in the satisfactory analgesia group (n = 30) was much longer than it was in the dissatisfactory analgesia group (n = 20) at 14.50 +/- 3.70 hours vs 5.90 +/- 2.12 hours. It means that patients whose pain was controlled in a satisfactory manner were in the need of secondary analgesia after a longer time. Moreover, the satisfactory analgesia group had significantly lower visual analog scale (VAS) score (1.60 +1.05) than the dissatisfactory one (3.10 +1.30), indicating that the former group received a better analgesia effect. Also, patients with satisfactory analgesia had fewer PCEA boluses (4.00 +/- 2.10) than patients with dissatisfactory analgesia (8.90 +/- 4.20), which means that all patients have a more effective and more lasting strategy of their pain management. These findings underline the disparities in the analgesic performance in the two groups, where the satisfactory analgesia one bore more pain control when deciding by the time to the first bolus, decreasing VAS levels, and the low number of required PCEA boluses.

Table 3: PCEA Data 24 hours After Elective Partial Hepatectomy

Variables	Satisfactory Analgesia (n = 30)	Dissatisfactory Analgesia (n = 20)
Time to the first PCEA bolus (h)	14.50 ± 3.70	5.90 ± 2.12

VAS score	1.60 ± 1.05	3.10 ± 1.30
Number of PCEA boluses	4.00 ± 2.10	8.90 ± 4.20

PCEA: Patient controlled epidural analgesia, VAS: visual analog scale

Discussion

Some studies indicate that adjuvant Prostigmin is additive or synergistic to both local anesthetics and opioids during the post-surgical period. Analgesia (dose-independent amount of around 8 hours) was induced by epidural Prostigmin 1, 2 or 4 mg as opposed to control group (around 3.5 hours) with lidocaine [2]. Orthopedic surgical patients received epidural morphine (0.6 mg) and epidural Prostigmin (60mg) combination to get postoperative analgesia of 11 hours without any side effect[3]. In recent studies of epidural Prostigmin combined with local anesthetics and opioids, positive effects were demonstrated even in the case of the administration of an epidural mixture consisting of Prostigmin with 10 mcg sufentanil in the treatment of labor pain or cesarean delivery and there was no negative effect on maternal and neonatal outcomes [5,13]. The dose-independent analgesia was achieved due to non-degradation of epidural Prostigmin in doses of 1 mg, 2 mg and 4 mg compared with the control group (around 3.5 hours) with lidocaine[2]. The study found that 0.6 mg of epidural morphine with 60 mg of epidural Prostigmin combination offered 11 hours of postoperative analgesia in orthopedic surgery patients without any side effects[3]. Also, combined doses of 500 mg epidural Prostigmin and 10 mcg sufentanil exhibited comparable positive outcomes in the recent epidural Prostigmin studies in association with local anesthetics and opioids, either during the process of labor analgesia or during cesarean sections, which showed no impact on functional consequences of the mother or the neonate [5,13].

It may be argued that the analgesic effect of epidural Prostigmin is because of its property to inhibit the degradation of acetylcholine in dorsal horn [14,15] and spinal meninges [16] once sufficiently crossed the dural barrier to access the cerebrospinal fluid (CSF). It is made by the analgesic effects of acetylcholine which is achieved by: 1) direct spinal cholinergic muscarinic M1 and M3 receptor stimulation [17]; 2) also, it was found that epidural Prostigmin might have analgesic actions mediated by the central cholinergic system [20]. It is also known that Prostigmin, a neuraxial medication, is safe and possesses muscarinic receptor mediated analgesia as is demonstrated by Eisenach JC , who stated that this medication prevented breakdown of acetylcholine and stimulated the dorsal horn of the spinal cord.

As shown in previous research[14, 22, 23], it has been shown that intrathecal Prostigmin was non-toxic and effective in relieving pain among animals and human beings. The intrathecal method was also constrained by the nausea that was experienced frequently (33-67) and vomiting (17-50) [24]. An interesting study conducted by Chia et al.[25] indicated that when 500 µg of epidural Prostigmin was administered before the surgery in a thoracotomy patient, and a continuous infusion of 17.5 µg/h was given during surgery, but stretched to the post operative period, preemptive and preventative analgesia was achieved. This regimen substantially lightened the severity of postoperative pain and exhibited the effect of the sparing analogue, which is a PCEA use, which has no effect on ramping up the side effects. Also epidural Prostigmin has the possible advantage of facilitating earlier recovery of bowel sound and prompt resolution of post-abdominal surgery ileus [26].

There are several limitations in this study. First, we assessed the quality of analgesia only at 8

and 24 hours after surgery, and our results lack comprehensive data on the long-term outcomes of the participants. Another limitation is the scoring system used; while the VAS score criteria are widely accepted, the criteria for time to the first PCEA bolus and the number of PCEA boluses were based on our pilot study and clinical practice. Additionally, one patient reported that the abdominal drain tube caused more pain than the abdominal incision itself. Future clinical studies are needed to determine whether the optimal dose of epidural Prostigmin in our study could improve outcomes for patients undergoing upper abdominal surgery without additional side effects. It is also important to note that the sample size limitations resulted in relatively wide 95% confidence intervals (CI) for ED50 and ED95 values.

Based on the findings above, we conclude that the ED50 and ED95 of epidural Prostigmin combined with PCEA for achieving satisfactory analgesia following partial hepatectomy were 228.63 ± 183 mg and 300.12 ± 224 mg, as determined using the Dixon up-and-down method. Epidural Prostigmin presents a promising alternative to traditional epidural antinociceptive drugs, providing satisfactory analgesia.

CONCLUSION

This article shows that the association of epidural Prostigmin and patient-controlled epidural analgesia (PCEA) has been an effective source of long term post-operative pain relief following partial hepatectomy. These findings report that 50 percent effective dose (ED50) of the drug is found to be 228.63 +/- 183 mg and effective dose on 95 percent (ED95) was identified at 300.12 +/- 224 mg and this was calculated using the Dixon up-and-down method. Epidural Prostigmin was found to significantly prolong time to first PCEA bolus, decrease number of PCEA boluses required, and deliver improved analgesia condition, in terms of the lower visual analog scale (VAS) scores, than the patients who had received unsatisfactory analgesia. The results favor a possible utility of epidural Prostigmin, as an appropriate addition to opioid, and local anesthetics mix in the control of postoperative pain. Nevertheless, the limitations of the study, such as small sample, and the absence of the long-term follow up results, require additional studies which would justify most appropriate dose of the drug, as well as evaluate the long-term potential benefits and harms of epidural Prostigmin in different surgical populations. Further research should also be aimed at determining whether epidural Prostigmin would be beneficial in enhancing the recovery rates, lowering the opioid use and when it comes to upper abdominal procedures, reducing side effects.

REFERENCES

1. Liu SS, Bieltz M, Wukovits B, John RS. Prospective survey of patient-controlled epidural analgesia with bupivacaine and hydromorphone in 3736 postoperative orthopedic patients Reg Anesth Pain Med. 2010;35:351–4

2. Pawlowski SA, Gaillard S, Ghorayeb I, Ribeiro-da-Silva A, Schlichter R, Cordero-Erausquin M. A novel population of cholinergic neurons in the macaque spinal dorsal horn of potential clinical relevance for pain therapy J Neurosci. 2013;33:3727–37

3. Lauretti GR, de Oliveira R, Reis MP, Juliâo MC, Pereira NL. Study of three different doses of epidural Prostigmin coadministered with lidocaine for postoperative analgesia Anesthesiology. 1999;90:1534–8

4. Omais M, Lauretti GR, Paccola CA. Epidural morphine and Prostigmin for postoperative

analgesia after orthopedic surgery Anesth Analg. 2002;95:1698–701
5. Roelants F, Lavand'homme PM. Epidural Prostigmin combined with sufentanil provides balanced and selective analgesia in early labor Anesthesiology. 2004;101:439–44
6. Nakayama M, Ichinose H, Nakabayashi K, Satoh O, Yamamoto S, Namiki A. Analgesic effect of epidural Prostigmin after abdominal hysterectomy J Clin Anesth. 2001;13:86–9
7. Kida K, Ohtani N, Shoji K, Yasui Y, Masaki E. Postoperative pain status after intraoperative systemic dexmedetomidine and epidural Prostigmin in patients undergoing lower abdominal surgery Eur J Anaesthesiol. 2008;25:869–75
8. Harjai M, Chandra G, Bhatia VK, Singh D, Bhaskar P. A comparative study of two different doses of epidural Prostigmin coadministered with lignocaine for post operative analgesia and sedation J Anaesthesiol Clin Pharmacol. 2010;26:461–4
9. Dixon WJ. Staircase bioassay: The up-and-down method Neurosci Biobehav Rev. 1991;15:47–50
10. Dixon WJ, Massey FJDixon WJ, Massey FJ. Sensitivity experiments Introduction to statistical analysis. 19834th ed New York McGraw-Hill:426–41
11. Choi SC. Interval estimation of the LD_{50} based on up-and-down experiment Biometrics. 1990;46:485–92
12. Ross VH, Pan PH, Owen MD, Seid MH, Harris L, Clyne B, et al Prostigmin decreases bupivacaine use by patient-controlled epidural analgesia during labor: A randomized controlled study Anesth Analg. 2009;109:524–31
13. Kaya FN, Sahin S, Owen MD, Eisenach JC. Epidural Prostigmin produces analgesia but also sedation in women after cesarean delivery Anesthesiology. 2004;100:381–5
14. Yaksh TL, Grafe MR, Malkmus S, Rathbun ML, Eisenach JC. Studies on the safety of chronically administered intrathecal Prostigmin methyl-sulfate in rats and dogs Anesthesiology. 1995;82:412–27
15. Abram SE, Winne RP. Intrathecal acetyl cholinesterase inhibitors produce analgesia that is synergistic with morphine and clonidine in rats Anesth Analg. 1995;81:501–7
16. Ummenhofer WC, Brown SM, Bernards CM. Acetylcholinesterase and butyrylcholinesterase are expressed in the spinal nitromeninges of monkeys and pigs Anesthesiology. 1998;88:1259–65
17. Naguib M, Yaksh TL. Antinociceptive effects of spinal cholinesterase inhibition and isobolographic analysis of the interaction with mu and alpha 2 receptor systems Anesthesiology. 1994;80:1338–48
18. Chiari A, Tobin JR, Pan HL, Hood DD, Eisenach JC. Sex differences in cholinergic analgesia I: A supplemental nicotinic mechanism in normal females Anesthesiology. 1999;91:1447–54
19. Xu Z, Tong C, Eisenach JC. Acetylcholine stimulates the release of nitric oxide from rat spinal cord Anesthesiology. 1996;85:107–11
20. Bartolini A, Di Cesare Mannelli L, Ghelardini C. Analgesic and antineuropathic drugs acting through central cholinergic mechanisms Recent Pat CNS Drug Discov. 2011;6:119–40
21. Eisenach JC. Muscarinic-mediated analgesia Life Sci. 1999;64:549–54
22. Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal Prostigmin methylsulfate in humans Anesthesiology. 1995;82:331–43
23. Eisenach JC, Hood DD, Curry R. Phase I human safety assessment of intrathecal Prostigmin

containing methyl- and propylparabens Anesth Analg. 1997;85:842–6
24. Liu SS, Hodgson PS, Moore JM, Trautman WJ, Burkhead DL. Dose-response effects of spinal Prostigmin added to bupivacaine spinal anesthesia in volunteers Anesthesiology. 1999;90:710–7
25. Chia YY, Chang TH, Liu K, Chang HC, Ko NH, Wang YM. The efficacy of thoracic epidural Prostigmin infusion after thoracotomy Anesth Analg. 2006;102:201–8
26. Caliskan E, Turkoz A, Sener M, Bozdogan N, Gulcan O, Turkoz R. A prospective randomized double-blind study to determine the effect of thoracic epidural Prostigmin on postoperative ileus after abdominal aortic surgery Anesth Analg. 2008;106:959–64