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Epidural pain management after open lateral thoracotomy: Female patients have better pain relief and need smaller amounts of analgesics than males

Gísli Vigfússon[a,*], Gísli H. Sigurðsson[a,b]

[a] Department of Anaesthesia & Intensive Care Medicine, Landspitali University Hospital, Iceland
[b] Faculty of Medicine, University of Iceland, Reykjavik, Iceland

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ABSTRACT

Background and aims: There is an ongoing dispute whether or not there is a gender difference in epidural drug requirements. The objective of this study was to compare the effects of a triple drug epidural mixture used for postoperative pain relief on male and female patients undergoing major surgery.
Materials and methods: To avoid possible influence of different age and type of surgery only 50–70 year old patients undergoing open lateral thoracotomy were included. 253 patients were enrolled: 116 males and 137 females. All patients received a mixture of bupivacaine 0.1 mg/ml, fentanyl 2 μg/ml, and adrenaline 2 μg/ml (BFA) by continuous infusion into the thoracic epidural space for postoperative pain relief. Infusion rate of the BFA solution was recorded and pain score was evaluated by numeric rating scale (NRS, 1–10) for 48 h post operatively.
Results: Adequate postoperative pain relief (NRS ≤ 3) at rest was accomplished in 91% of male patients on day one and 92% on day two and by 94% and 100% of female patients, respectively. Females had significantly lower median pain scores than males on day two both at rest ($P < 0.011$) and by movement ($P < 0.012$). In addition females required significantly smaller amounts of BFA mixture ($P < 0.01$) and less frequently rescue opioids ($P < 0.025$) than males.
Conclusion: Female patients had significantly better pain relief both at rest and by movement, needed smaller amounts of the epidural bupivacaine, fentanyl, adrenaline mixture for postoperative pain relief and received less frequently rescue opioids than males.
Implications: The dose of thoracic epidural infusion of low-concentration bupivacaine-, fentanyl-, and adrenaline-solution should routinely be set lower for postmenopausal women than for elderly male patients during and after thoracotomy.

1. Introduction

Postoperative pain management with continuous epidural analgesia has been shown to have several advantages over traditional pain treatment after major surgery [1]. Many factors have been shown to affect efficacy of drugs administered epidurally for postoperative pain relief [2–5]. However, the literature is still controversial concerning the influence of gender [6–9]. It has been suggested that there is a gender difference concerning the effect of opioids after surgery [6]. The reasons for such difference could be multifactorial, such as hormonal, variable sensitivity of opioid receptors, as well as hereditary and psychological [2,10]. In clinical trials on post-operative analgesic requirements, the results have differed, some showing benefits for females and others for males [7–9]. Very few studies have focused on gender differences of epidural anaesthesia [7,9] and none has standardized such important factors as the surgical trauma and patients age. At our institution postoperative pain management with continuous epidural infusion of a triple drug mixture (bupivacaine 0.1 mg/ml, fentanyl 2 μg/ml, and adrenaline 2 μg/ml; BFA) has been used after major surgery for more than a decade [11] and the clinical routine has not changed during this time period. Clinical data from these patients was simultaneously recorded and stored in the hospital database. The aim of this study was to investigate whether there was difference between females and males in the effects of epidural anaesthesia used for postoperative pain control in patients undergoing standardized major surgery (lateral thoracotomy) at a relatively narrow age range (50–70 years old). Our hypothesis was

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* Corresponding author at: Department of Anaesthesia & Intensive Care Medicine, Landspitali University Hospital, Hringbraut, IS 101 Reykjavik, Iceland.
Tel.: +354 543 7348/1000.
E-mail address: gislivig@landspitali.is (G. Vigfússon).

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Table 1
Group characteristics.

Patients	Mean age (range)	Number of patients	Height (cm) (range)	Weight (kg) (range)	BMI (kg/m^2) (range)
Males	62.0 (50–70)	116	178.9 (156–198)	85.9 (58–135)	26.86 (19–38)
Females	60.7(50–70)	137	165.2 (150–182)	71.1 (48–110)	26.08 (17–41)

Mean age, number of the patients, height, weight and body mass index (BMI) in each group.

that post menopausal women receiving continuous epidural anaesthesia with BFA after major thoracic surgery experience less pain than men at the same age.

2. Materials and methods

The ethics committee of Landspitali University Hospital approved the study protocol. All patients in the hospital database during the years 1996–2009 who fulfilled the following criteria were entered into the study: patients who had open lateral thoracotomy, aged 50–70 years and received continuous epidural infusion of a triple drug mixture containing bupivacaine 0.1 mg/ml, fentanyl 2 μg/ml, and adrenaline 2 μg/ml for postoperative pain relief. We chose major thoracic surgery since thoracotomy is known to result in severe pain when the patient moves or coughs.

During this 12 year period virtually no changes were made in the treatment protocol for postoperative epidural pain relief after major surgery in our department. According to the departmental clinical practice protocol the epidural infusion rate was titrated to a pain score ≤3 on a 10 numeric rating scale (NRS-11) at rest and mild pain when coughing. However if there was leg weakness the infusion rate was reduced. If the patient complained of pain the infusion rate of the triple drug epidural mixture was increased except if the level of the epidural anaesthesia was considered adequate. In that case morphine 2.5–5 mg or occasionally a nonsteroidal-antiinflammatory-drug (NSAID) agent was administered at the discretion of the ward nurse.

Anaesthesia and surgery data were accessible in the hospital database and data concerning pain scores at rest and by movement/coughing as well. Epidural drug mixture infusion rate, administration of rescue drugs, and adverse effects were recorded by all patients by specially trained ward nurses on a special data sheet. All patients received paracetamol 1 g 6 hourly rectally or orally. A nurse from the department of anaesthesia collected these data records and entered the data into the hospital data base. Although the protocol and registration of patient data were mainly made for the purpose of quality control this was also meant to serve as a database for scientific research.

In order to reduce the possible effects of other factors, such as different types of surgery, premenopausal effects and age differences, only females and males between 50 and 70 years of age undergoing open lateral thoracotomy were selected for the study.

The epidural protocol: an epidural catheter was inserted segmentally at T_4–T_7 before induction of anaesthesia and epidural treatment was initiated during surgery and continued postoperatively for 4–6 days. The triple drug epidural anaesthetic solution contained bupivacaine 1 mg/ml, fentanyl 2 μg/ml and adrenalin 2 μg/ml ("Standard EDA-blanding", Kabi Fresenius, Norway).

Pain at rest and during coughing was assessed on the first and second postoperative days by the attending nurse in the ward according to the 0–10 numeric rating scale (NRS). The infusion rate per kg and per BMI was recorded on the second postoperative day. The need for additional analgesics, opioids and or non steroidal anti inflammatory drugs (NSAID) was recorded during the observation period. A statistical comparison was made between the two groups (males and females) as regards pain at rest and during coughing on the first and second days, infusion rate of the epidural analgesics (based on body mass index, BMI) during the observation period using two sided Studentĭs *t*-test. The percentage of patients receiving adequate postoperative pain relief (NRS ≤ 3) at rest and by movement as well as the frequency of rescue opioids and NSAIDs was compared using Fisherĭs exact test. The Bonferroni correction was used to adjust for multiple comparisons in all statistical analysis. $P < 0.05$ was considered statistically significant.

Table 2
Indications for open lateral thoracotomy.

Diagnosis	Males	Females
Bronchiectasia/pneumothorax	8	9
Lobectomy	95	112
Pulmectomy	7	6
Lat. thoracotomy unspecified	6	10

Table 3
Level of epidural puncture.

Level of epidural puncture	Males	Females
$T_{4–5}$	8	12
$T_{5–6}$	42	55
$T_{6–7}$	47	47
$T_{7–8}$	15	15
$T_{8–9}$	4	6
$T_{9–10}$	0	2

A similar number of patients had epidural puncture in the segmental position T_4–T_7 in both groups.

3. Results

The total number of patients who fulfilled the study criteria was 321, 180 females and 142 males. 38 females and 25 men had insufficient data, concerning height and weight and were excluded from the analysis. In addition, registration into the database was incomplete for 6 females and 1 male. As a result, 137 women and 116 men were included in the analysis (Table 1). As shown in Table 2, the majority of patients underwent lung tumour surgery involving lobectomy or pulmectomy. Similar number of patients in both groups underwent lateral thoracotomy because of repeated pneumothorax or other conditions. A similar number of patients had the epidural in the segmental position T_4–T_7 in both groups (Table 3). In both groups, acceptable pain relief was achieved by >90% of patients at rest on postoperative days 1 and 2 (Table 4).

On the first postoperative day similar number of patients in both groups had adequate pain relief during movement/coughing and did not require rescue drugs. More patients had acceptable pain relief on day two than on day one in both groups. There was a statistically significant difference between the groups on the second

Table 4
Postoperative analgesia.

Analgesia at rest and by movement/coughing	Males (%)	Females (%)
First day: NRS ≤ 3 at rest	91	94
First day: NRS ≤ 3 by movement	66	69
Second day: NRS ≤ 3 at rest	92	100
Second day: NRS ≤ 3 by movement	75	89

Pain relief by NRS ≤ 3 at rest and by movement on first and second postoperative day. There was a significant difference between males and females on day two both at rest ($P < 0.011$) and by movement ($P < 0.012$).

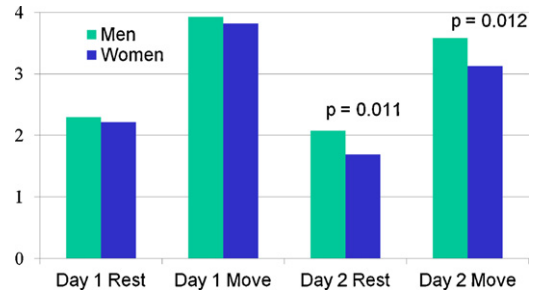

Fig. 1. Mean postoperative pain scores on day one and two. Day 1 rest: pain score on day one at rest. Day 1 move: pain score on day one by movement (coughing). Day 2 rest: pain score on day two at rest. Day 2 move: pain score on day two by movement (coughing).

day regarding pain relief (Table 4; Fig. 1). When considering the body mass index the females required significantly lower infusion rate of the epidural BFA solution ($P < 0.01$), and less rescue opioids ($P < 0.05$) than the males (Table 5).

4. Discussion

This study shows that women aged 50–70 years need significantly smaller amounts of the epidural triple-drug solution containing bupivacaine 1 mg/ml, fenatnyl 2 μg/ml, and adrenaline 2 μg/ml (BFA) than men at the same age for pain relief after thoracotomy. Despite smaller amounts of drugs women had significantly better pain relief on the second postoperative day both at rest and during movement. In addition they also needed smaller amounts of opioid rescue drugs.

It is suggested that this difference between the two groups studied is explained by gender because other factors that could influence the results were largely controlled including the distribution of surgical procedures which was comparable in the two groups and the epidural catheter was in 95% of cases optimally placed between T_4 and T_7 in both groups [12].

At our hospitals this triple-drug epidural mixture for pain relief during and after thoracic surgery has been used for two decades. The drug combination used is based on extensive experience from Norway and Switzerland [11]. It consists of bupivacaine 1 mg/ml, fentanyl 2 μg/ml and adrenaline 2 μg/ml. The synergistic analgesic effects of these three drugs in the spinal dorsal horn have been demonstrated [11,13]. In addition, the adrenaline in the mixture causes vasoconstriction, of epidural vessels, but not of subarachnoid vessels supplying the spinal cord, which delays absorption into epidural vessels, increases the amount of active drugs reaching the spinal cord, the most important site of action, prolongs efficacy, and reduces side effects such as nausea, pruritis, urinary retention, and bleeding in the epidural space [13,14].

We decided to include only patients that had undergone open lateral thoracotomy, usually for lung tumours into this study. This is a fairly standardized major surgical trauma and is known to result in severe pain when the patient moves or coughs. Therefore it served the purpose of this study. We also only included patients between 50 and 70 years of age in order to minimize the possible influence of age on the results. It is known that age [4,5] and pre- and postmenopausal period [10] can influence the effects of analgetic drugs.

Thus by choosing only patients aged between 50 and 70 and standardising the surgical trauma we had fairly homogenous groups of patients that should allow us to evaluate if there was a gender difference in epidural drug requirements. To our knowledge this is the first study that has standardized these important factors and therefore we believe that our results are reliable. This study was not designed to determine which part of the epidural triple drug solution had particular effects by females or males.

Previous studies both experimental and clinical have shown conflicting results concerning gender difference of analgetic agents [2–9,15–20]. It appears that reproductive hormones affect the sensitivity of different opioid receptors in the nervous system [2] and genetic effects may also play a role [16,17].

A number of clinical studies have been performed where the difference in the use and efficacy of opioids has been examined according to the gender of the patients. As in animal studies, the results of clinical studies have differed on the various advantages for males and for females. However, a recent metaanalysis showed that sex differences exist in morphine-induced analgesia in both experimental pain studies and clinical (and intravenous opioid patient controlled analgesia (PCA)) studies, with greater morphine efficacy in women [21]. A large prospective clinical study also showed greater use of opioids in men than women [8]. Many of these studies have been criticised for assessing opioid use and not pain effects and for not having made corrections for height and weight.

A pharmacokinetic/dynamic study of volunteers showed that morphine had greater efficacy in women than men, although women required higher initial doses than men [23]. This larger initial dose is attributed to slower flow of the drug over the brain threshold in women than in men, which therefore necessitates a higher dose for women at the beginning of treatment [15,22,23]. This could be one of the reasons why there was a greater difference in pain relief between females and males on day two than on day one after surgery in the present study.

Our results are in contrast to those of Chang et al. [9] In a study using patient controlled epidural analgesia with fentanyl and bupivacaine for postoperative pain relief, they found no gender difference after chest, abdomen or lower extremity surgery [9]. However, the authors did not report different types of thoracic surgery nor different age groups. In a study by Ochroch et al. pain experience and the requirement of epidural anaesthesia drugs was greater in females than in males after chest surgery [7]. In that study the patients received high doses of fentanyl, 10 μg/ml epidurally in the postoperative period. It has been shown that when fentanyl is administered epidurally in a concentrated solution without adrenaline, it is absorbed more rapidly into blood stream and the epidural effect can be confounded by the systemic effects [24,25]. Furthermore in this study [7] females were significantly younger (5 years) than the males. In addition it was not clear how many females were in premenopausal age, which may have confounded the results [4,10].

Table 5
Use of epidural drug mixture and rescue drugs.

Analgesia at rest and by movement/coughing	Males	Females
Median BFA infusion rate on day two in ml/BMI/h (range)	0.303 (0.10–0.55)	0.272 (0.13–0.59)
Median BFA infusion rate on day two in ml/h	8.1	7.1
Patients receiving rescue opioid drugs %	39	28
Patients receiving rescue NSAID %	41	39

Administration rate of epidural drug mixture (BFA) on day two (the median of the average of each patient during 24 h) and the use of rescue drugs on day two postoperatively. The difference in administration rate of epidural drug mixture between males and females was statistically significant ($P < 0.01$). NSAID: none steroidal anti-inflammatory drugs. The difference in opioid use between males and females was statistically significant ($P < 0.025$).

5. Conclusion

During postoperative thoracic epidural analgesia using a mixture of low concentrations of bupivacaine, fentanyl (2) and adrenaline females aged 50–70 years required significantly smaller amounts of rescue analgesics and had significantly better postoperative pain relief at rest and during movement than males at the same age.

6. Implications

The dose of thoracic epidural infusion of a low-concentration bupivacaine-, fentanyl-, and adrenaline-solution should routinely be set lower for postmenopausal women than for elderly male patients during and after thoracotomy.

Conflict of interest

None of the authors has any conflicts of interest to declare.

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