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Pain Relief Methods after Thoracotomy

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ABSTRACT

Background: Thoracotomy is one of the surgical operations which causes severe pain. In fact, this pain is one of the most excruciating pains caused by surgical operations.

Different procedures are performed to decrease this pain which is associated with significant physiologic, mental and pathologic complications. Each of these procedures has its own advantage and disadvantages.

In many centers, the most common treatment method used, is considered as the first choice. In this study, common methods of analgesia after thoracotomy were compared.

Materials and Methods: During this meta-analysis, "Visual Analogue Scale" (VAS) of patients in epidural group was compared with those in four groups of systemic opioids, intercostal block, para-vertebral block and intrapleural infusion in the first 24 hours after surgery.

Data obtained from 28 randomized clinical trials (RCT) which compared the procedures in 1697 patients after thoracotomy were gathered using random effect model, effect size index and the standardized difference average. Statistical values were evaluated and the results obtained using standard error, 5% maximum confidence limit and 5% minimum confidence limit. The obtained data were evaluated using studies performed between 1987 and 2005.

After evaluating 314 titles and 185 abstracts, 28 articles were entered in the meta-analysis considering inclusion criteria. Four groups of epidural with systemic opioids, epidural with para-vertebral, epidural with intercostal and epidural with intrapleural analgesia were studied.

Results: It was noticed that the epidural method in total 24 hours with 95% CI= -0.9802 to -0.3844 was a better procedure compared with systemic opioids. Epidural method did not show any difference with intercostal method in 24 hours mean with 95% CI= -0.2171 to +0.5906. Epidural method was also better than intrapleural in 24 hours mean with 95% CI= -1.1166 to -0.0106. When comparing epidural with para-vertebral, epidural was better with 95% CI= +0.1744 to -0.4527.

Conclusion: According to the evaluations performed, epidural method is recommended as the method of choice to reduce pain after thoracotomy. (Tanaffos 2005; 4(16): 29-39)

Key words: Analgesia, Thoracotomy, Procedure

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INTRODUCTION

Thoracotomy is a surgical operation associated with severe postoperative pain. This pain not only bothers the patient but also has many physiologic and pathologic complications that affect the prognosis and outcome of surgery.

Patients try to move less because of pain leading to shallow breathing which causes hypoxia and pulmonary dysfunction.

Pulmonary dysfunction after surgery can delay the healing process and threatens the patient's life.

Hypoxia can also delay healing of lesion and causes cognitive disorders.

Immobility causes atelectasis which makes the patient susceptible to infection and pulmonary insufficiency (1).

Severe postoperative pain is one of the significant complications of this operation and many efforts have been made in this regard. These include different analgesic procedures using systemic or local (regional) methods. Each of these has their own advantages and disadvantages.

The more common ones are: using intravenous drugs such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or regional methods such as using anesthetic drugs or opioids inside the epidural or spinal spaces, using intercostal nerve blocks, anesthetic infiltration inside the lesion, para-vertebral blocks, opioids infusion or intrapleural anesthetic drugs and cryoanalgesia.

In most studies, a specific method has been compared with another one and the analgesic effect and complications of two or three methods are evaluated.

In order to ascertain which procedure has the best effect, data obtained from these comparisons must be combined, which has not been performed till now and each center has selected one method as the method of choice considering its own conditions (2).

By using meta- analysis, various studies having

comparable characteristics are compared with each other.

DIFFERENT METHODS OF ANALGESIA

Systemic Analgesia:

This is one of the most common procedures causing analgesia after surgery. In fact, the traditional method of postoperative analgesia is intravenous or intramuscular injection of opioids. Major problem in using this method is the narrow therapeutic window of drug. Average doses cause side effects including nausea, vomiting, drowsiness, itching, respiratory distress and etc.

The last complication is usually the most important one which is often the most important complication especially after general anesthesia and might be due to remaining of the vaporizing anesthetic effect of drugs and is accompanied by pulmonary dysfunction.

This is generally a simple method with its own complications. This is why in many researches this method has been compared with other methods of analgesia and different results have been obtained in which the quality of analgesia and complications have been compared with those of other procedures.

Regional analgesia:

This type of analgesia includes intercostal blocks, epidural blocks, para-vertebral blocks, intraspinal blocks, intrapleural blocks and cryoanalgesia.

- Epidural analgesia:

This method is described as injecting the opioid or local anesthetic drug into the epidural space. In this method we reach the epidural space by a particular procedure using a special needle and drug will be injected in this area.

In this method, a catheter enters the space during or after the operation and drug is injected through this after the surgery.

This catheter can enter the lumbar or thoracic space and the drug (opioid, local anesthetic or both) will be injected through it. This is a common method of analgesia as well.

Optimal analgesia and lesser drug complications are of the advantages of this method (1,3) .

Complications of this method mainly include: systemic complications of drugs (opioid complications) such as nausea, vomiting, itching, respiratory depression or complications of the local anesthetic drugs such as tinnitus, seizure and cardiovascular toxicity, and complications due to sympathetic block such as hypotension, urine retention and etc.

Wrong injection due to displacing the catheter tip into the spinal space or into the veins is another complication of this method. A pump can be used as patient-controlled or infusion for drug injection.

In many centers, epidural method is used as the method of choice because of optimal analgesia and possibility of using catheter after the operation (1, 4).

Numerous studies have been performed regarding the epidural as the best method of analgesia compared with other methods. Most of these researches have been conducted in the form of comparing two or three different methods with each other or as a systematic review which various results have been obtained (3,4,5,6).

- Intercostal nerve block:

In this method, intercostal nerve is blocked at the site by using local anesthetic drugs during or after the surgery. In this procedure, some other nerves superior or inferior to the incision site are usually anesthetized.

Some of the advantages of this procedure are optimal analgesia and its simple technique, but rapid absorption of the anesthetic drug usually occurs which is associated with the risk of drug toxicity and pneumothorax.

Another disadvantage of this procedure is the need for frequent injections. To obviate this difficulty, extra pleural catheters are used.

Many researchers have compared this procedure with other methods and some considered this as a proper method for analgesia after thoracotomy.(6)

- Intrapleural block:

Intrapleural analgesia is resulted from placing a catheter into the pleural space between the parietal and visceral pleura.

This method was first presented in 1981 by Reiestoal and Kvalhemi and the results were reported in 1986. This method has been used successfully to relieve pain after cholecystectomy, kidney and breast surgeries and reducing the pain due to rib fractures (7, 8).

Analgesia results by diffusing the drug from the pleural space through parietal pleura and intercostal muscles to the intercostal space and blocking the nerves.

The effect of intrapleural injection of opioids is based on activation of the opioid receptors on the intercostal nerves directly by the opioid so that the pain is decreased (9, 10, 11).

Complications of this method including complications of local anesthetic drugs and/or opioids are either due to the block of thoracic sympathetic chain or phrenic nerve palsy (9, 10, 12).

This method is simple to perform and results in an optimal analgesia. Therefore, many researchers have compared this method with other common methods of analgesia such as systemic prescription of opioids or intercostal and epidural blocks; and have reported interesting results in this regard.

- Para-vertebral block:

Para vertebral block is usually performed by entering a needle into the para-vertebral space. Placing the para-vertebral catheter is possible during the surgery and under direct supervision of the

surgeon before the operation or after it.

This method was first used by Hugo Sellhiem in 1905, (13) and is often performed unilaterally. Therefore, it is mainly used in unilateral surgeries such as lateral thoracotomy, cholecystectomy, hernia and kidney surgeries as well as thoracic trauma. However, it sometimes might be used bilaterally as well. This method results in an optimal analgesia during or after the operation. It is quite simple and catheter can be used as well. There is also a minor possibility of side effects in this method.

This type of analgesia is contraindicated if any of the following conditions exists:

- Presence of regional sepsis at the site of injection
- Presence of tumor at the site of injection
- Presence of tumor at the site of injection in paravertebral space (13)

Side effects of this procedure (which are less than 5%) (13) are: possible failure, hypotension, intravascular injection, intrapleural injection and pneumothorax. Unilateral Horner's syndrome may occur by increased level of block.

Some researchers are in favor of using this method for analgesia after thoracotomy and have compared it with other methods including intravenous opioids, epidural block and... (13).

- Cryoanalgesia:

Cryoanalgesia is also one of the non pharmaceutical methods of analgesia after thoracotomy. This method was first introduced by Liloyd and his colleagues in 1976 (14).

In this method, the temperature of nerve is decreased to -20°C during the operation under direct supervision using a probe and an inclusion of nervous tissue is formed inside a frozen ball which causes a nerve block for almost 6 months. In this procedure usually a nerve at the incision site, one superior to the incision and one inferior to it are frozen.

This procedure is mainly used in cases in whom long term pain is expected. Cryoanalgesia has turned into one of the main complementary methods of analgesia after thoracotomy as the result of strong pain relief and long-term analgesia (2).

This method is non-expensive and simple to perform, resulting in long term analgesia.

Risks of possible anesthesia and numbness or hyperesthesia at the site are of the disadvantages of this procedure that may last for 2 to 3 months.

Another advantage of this method is the absence of any drug usage; therefore, there would be no risk of toxicity by opioids or local anesthetics.

In some studies this method has been compared with others and various reports have been published in this regard (1).

In most of them, these methods have been compared as two studies compared with each other or one comparing with the control group and a limited number of patients in these groups have been evaluated.

The question "Which of these procedures can result in a more favorable analgesia?" will be answered by evaluating all these procedures together.

REVIEW OF LITERATURES

Considering the importance of this subject, numerous researches have been performed in the field of postoperative analgesia and as we mentioned before, they were mostly comparative studies. Generally, there was no research as a meta-analysis to specifically study the analgesia after surgery (Searching Medline, Google, Elsevier and reliable accessible journals).

In 1998, a study was performed by Ballantyne and colleagues regarding methods of postoperative analgesia in which the effects of these procedures on patient's pulmonary function were evaluated (1).

It was a cumulative meta-analysis with no curve

for analgesic effects of these methods.

Most of these researches in this regard have been reported as review article; among them, a few have been mentioned here (2,4,6,15-26).

Another meta-analysis was conducted in 2004 in which the effect of some analgesic methods (some drugs) were evaluated as preemptively and postoperatively (27).

An interesting point in this meta-analysis was the optimal analgesic effect of epidural preemptively which had not been seen in NSAIDs and opioids.

Also, doses of opioids and NSAIDs used in epidural local anesthesia were smaller when used preemptively (comparing postoperatively).

In a study by Richardson et al. in 1999, the effect of analgesic methods on pulmonary tests was evaluated and the para-vertebral method was selected as a method with the best pulmonary outcome (21).

Main Object:

The aim of this study was to compare the effects of analgesic methods after thoracotomy.

In this study randomized clinical trial were used and the obtained data were combined to find out whether these methods differ from each other and to see which one is better (meta-analysis).

Specific objects of this study were to compare analgesia in the first 24 hours after thoracotomy (in different hours) in the epidural method with systemic opioids, and with para-vertebral, intrapleural and intercostal blocks.

MATERIALS AND METHODS

The main variable in this study is the severity of pain after surgery which was measured by "Visual Analogue Scale" (VAS) and has been used in all studies evaluated (28).

Another variable was the time at which pain was evaluated after surgery. In most studies, the pain has been evaluated and noted at the first, fourth, eighth,

twelfth, sixteenth, and 24th hour after surgery.

In this study, articles regarding thoracotomy pain from 1987 to 2005 were evaluated using all accessible sources. Articles used in this study had the following criteria:

- 1- All were randomized clinical trials.
- 2- All were blind studies.
- 3-VAS had been used in all of them.
- 4- Minimum sample size was 10 or more.

All manuscripts had the above mentioned criteria; therefore, the study quality was considered the same in all of them.

A total of 25 manuscripts were used in meta-analysis and 1697 patients in 4 groups were compared with each other regarding postoperative pain.

After classifying the data obtained from comparative studies, differences of means were calculated and a new difference average was obtained using random effect model. Probability level of difference average was calculated separately for each hour in both direct and indirect stages using the Chi-square test. (By using non-directional zero-effect model it will be proved whether any difference exists between the methods)

If, even in one case $P\text{-value} < 0.05$, the effects of two methods of analgesia are not the same.

In the direct zero-effect model it is evaluated whether the difference in the two groups is the same.

Then, by obtaining the standard error, 95% upper confidence limit and 95% lower confidence limit for each hour and for the total hours as well, the significance of the understudy method was evaluated using CI.

In fact, if the distance between the upper and lower confidence limits is above or below zero (not including zero itself) the difference between the two groups is significant. (e.g. If VAS in one group is totally higher, the quality of analgesia in that group is lower). But, if the distance between upper and lower

confidence limits includes zero, no significant difference exists between the two methods under study.

RESULTS AND DISCUSSION

These methods were compared with each other and the obtained results were recorded in related tables 1-9.

Table 1. Comparison of epidural method with systemic opioids.

Number of comparisons	Reference number	Time of evaluation	variable	Difference average	95% lower confidence limit	95% Upper confidence limit
10	28-29-37	1	VAS	-0.7022	-1.6044	0.200
6	29-32-33-34-37	4	VAS	-0.5942	-1.65	0.4708
6	29-30-31-32-35-36	8	VAS	-0.2934	-1.28	-0.7067
7	28-29-32-37	12	VAS	-0.3789	-0.132	0.3747
4	30-31-34-36	16	VAS	-0.3703	-1.23	0.3851
10	28-37	24	VAS	-1.40	-0.98	-0.48
	Overall				-0.98	-0.3484

Table 2. Results of the comparison between epidural method and systemic opioids.

Method	Time of evaluation						
	At 1 st hour	At 4 th hour	At 8 th hour	At 12 th hour	At 16 th hour	At 24 th hour	In total 24 hours
Epidural	NS	NS	+	NS	NS	+	+
Systemic opioids	NS	NS	-	NS	NS	-	-

+ : More advantageous
 - : Less advantageous
 NS: No Significant

Table 3. Comparison of intercostal with epidural block (primary data)

Number of comparisons	Reference number	Time of evaluation	variable	Difference average	95% lower confidence limit	95% Upper confidence limit
3	38-40	4	VAS	0.3996	-0.585	1.385
3	38-40	8	VAS	-0.1642	-1.02	0.6971
3	38-40	12	VAS	1.039	0.5991	1.4897
1	39	16	VAS	1.039	0.5995	1.4897
3	41	24	VAS	-0.4725	-0.79	-0.151
	Overall		VAS	0.1868	-0.2171	0.5906

Table 4. Final comparison of the effects of epidural and intercostal methods on VAS.

Method	Time of evaluation					
	At 4 th hour	At 8 th hour	At 12 th hour	At 16 th hour	At 24 th hour	In total 24 hours
Intercostal	NS	NS	-	-	+	Ns
Epidural	NS	NS	+	+	-	NS

+ : More advantageous
 - : Less advantageous
 NS: No Significant

Table 5. General comparison of epidural and intrapleural methods

Number of comparisons	Reference number	Time of evaluation	variable	Difference average	95% lower confidence limit	95% Upper confidence limit
2	44-46	1	VAS	0.068	-2.0553	2.4489
5	42-43-45-46-47	4	VAS	0.0120	0.0465	1.9535
6	42-47	8	VAS	-0.0216	-1.98	0.1410
1	46	12	VAS	0.1968	-2.055	2.448
3	43-44-47	16	VAS	-1.33	-2.684	-0.0117
5	42-43-44-45-47	24	VAS	-0.78	-1.7345	0.1672
	Overall			-0.3636	-1.1166	-0.0106

Table 6. Final comparison of epidural and intrapleural methods

Method	Time of evaluation						
	At 1 st hour	At 4 th hour	At 8 th hour	At 12 th hour	At 16 th hour	At 24 th hour	In total 24 hours
Intrapleural	NS	NS	NS	NS	NS	NS	-
Epidural	NS	NS	NS	NS	NS	NS	+

+ : More advantageous
 - : Less advantageous
 NS: No Significant

Table 7. General comparison of paravertebral and epidural methods

Number of comparisons	Reference number	Time	variable	Difference average	95% lower confidence limit	95% Upper confidence limit
3	49-50-51	4	VAS	0.804	0.0866	1.5217
4	48-49-50-51	8	VAS	0.80	0.0091	0.9909
2	48-50	12	VAS	0.6516	-0.3238	1.026
4	48-49-50-51	16	VAS	0.0311	0.638	0.7006
2	49-50	20	VAS	0.19883	0.1483	0.2483
4	48-49-50-51	24	VAS	0.3489	-0.7620	1.4598
		overall	VAS	0.3136	0.1744	0.4527

Table 8. Final comparison of paravertebral and epidural methods

Method	Time of valuation							
	At 1 st hour	At 4 th hour	At 8 th hour	At 12 th hour	At 16 th hour	At 20 th hour	At 24 th hour	In total 24 hours
Epidural	NS	+	NS	NS	NS	+	NS	+
Paravertebral	NS	-	NS	NS	NS	-	NS	-

+ : More advantageous
 - : Less advantageous
 NS: No Significant

Another method which is rarely used is cryoanalgesia which is usually used when there is a possibility of long term pain. First we managed to use it in the meta-analysis but after searching the articles and abstracts it was understood that there were limited number of accessible articles and they had not any inclusion criteria for meta-analysis (no validity score).

Therefore, we only mentioned the abstracts here and the results were presented as review (table 9).

Table 9. Comparison of cryoanalgesia method in a few studies performed

Author	Year	Comparison types	Advantageous	Number	Reference
D Yi Jun	2005	Cryo - PCEA	NS	20-20	52
Yang MK	2004	Cryo- epidural and epidural alone	-	45-43	53
Moorjani	2001	Histologic study to reduce chronic pain	+	200	54
Brichon	1994	Cryo- intercostals-epidural	+	40-40-40	55
Miguel	1993	Cryo- epidural	-	15-15	56
Berrisford	1990	Cryo and control	-	63	57
Joucken	1987	Cryo- intercostal and control	NS	?	58
Roxburgh	1987	Cryo and control	NS	53	59

In evaluating 4 groups of meta-analysis the results were as follows:

In comparison between the epidural and systemic opioid methods, the epidural method had a better pain relief at the 8th and 24th hour but there was no statistically significant difference at the first, 4th, 12th and 16th hour. In total 24 hours, epidural method had a better pain relief. In comparison between the epidural and para-vertebral methods, epidural had a better pain relief at the 4th and 20th hour. There was no significant difference at 8, 16 and 24th hour between the two groups but epidural method was

better in this regard in total 24 hours.

In comparison between the two methods of epidural and intercostal, intercostal was better in 24th hour time, epidural was better at the 12th and 16th hour time and there was no difference at 4th and 8th hour time. In total 24 hours there was no significant difference between the epidural and intercostal methods regarding pain relief.

In comparison between the intrapleural and epidural methods, in total 24 hours mean epidural group showed a better pain relief (although we could not report the difference at 1,4,8,12,16 and 24th hours because it was not statistically significant).

Evaluating cryoanalgesia (comparing cryoanalgesia with other groups or with the control group) in one study, cryoanalgesia was better compared with intercostal but weaker comparing with epidural. In 3 other studies the difference was not statistically significant. In 3 studies cryoanalgesia was weaker than the control.(52,59)

Conclusion

According to the evaluations performed, epidural method is recommended as the method of choice to reduce pain after thoracotomy. Of course, it must be mentioned that this study only focused on “pain” and other advantages or disadvantages of methods are not considered.

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REFERENCES

1. Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* 1998; 86 (3): 598- 612.
2. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991; 324 (21): 1445- 50.
3. Kavanagh BP, Katz J, Sandler AN. Pain control after thoracic surgery. A review of current techniques. *Anesthesiology* 1994; 81 (3): 737-59.
4. Cook TM, Riley RH. Analgesia following thoracotomy: a survey of Australian practice. *Anaesth Intensive Care* 1997; 25 (5): 520- 4.
5. de Leon-Casasola OA, Lema MJ. Postoperative epidural opioid analgesia: what are the choices? *Anesth Analg* 1996; 83 (4): 867- 75.
6. Soto RG, Fu ES. Acute pain management for patients undergoing thoracotomy. *Ann Thorac Surg* 2003; 75 (4): 1349- 57.
7. Management of post op pain. Benumof JL ed. Anesthesia for thoracic surgery. Philadelphia, Pennsylvania: WB. Saunders Company, 1995. P: 755-7.
8. McIlvaine WB. Pro: intrapleural anesthesia is useful for thoracic analgesia. *J Cardiothorac Vasc Anesth* 1996; 10 (3): 425- 8.
9. Welte M, Haimerl E, Groh J, Briegel J, Sunder-Plassmann L, Herz A, et al. Effect of interpleural morphine on postoperative pain and pulmonary function after thoracotomy. *Br J Anaesth* 1992; 69 (6): 637- 9.
10. Aykac B, Erolcay H, Dikmen Y, Oz H, Yillar O. Comparison of intrapleural versus intravenous morphine for postthoracotomy pain management. *J Cardiothorac Vasc Anesth* 1995; 9 (5): 538- 40.
11. Dhokarika P, Caywood DD, Stobie D, Raffe MR, Albrecht M, Kannan M, et al. Effects of intramuscular or interpleural administration of morphine and interpleural administration of bupivacaine on pulmonary function in dogs that have

- undergone median sternotomy. *Am J Vet Res* 1996; 57 (3): 375- 80.
12. Khor KE, Josephson MA. Blood-stained pleural effusion complicating interpleural analgesia. *Acta Anaesthesiol Scand* 1995; 39 (2): 270- 2.
 13. Richardson J, Lonnqvist PA. Thoracic paravertebral block. *Br J Anaesth* 1998; 81 (2): 230- 8.
 14. Lioyd JW, Barnard JD, Glynn CJ. Cryoanalgesia. A new approach to pain relief. *Lancet* 1976; 2 (7992): 932- 4.
 15. Peeters-Asdourian C, Gupta S. Choices in pain management following thoracotomy. *Chest* 1999; 115 (5 Suppl): 122 S- 124 S.
 16. Clare Savage. Post thoracotomy pain management. *Chest surg clin N Am* 2002; 12: 251-63.
 17. Karager Marelise. Post thoracotomy pain control. *Current opinion in Anesthesiology* 1999; 12(1): 55.
 18. Lubenow TR, Faber LP, McCarthy RJ, Hopkins EM, Warren WH, Ivankovich AD. Postthoracotomy pain management using continuous epidural analgesia in 1,324 patients. *Ann Thorac Surg* 1994; 58 (4): 924- 9; discussion 929- 30.
 19. Sandler AN. Post-thoracotomy analgesia and perioperative outcome. *Minerva Anesthesiol* 1999; 65 (5): 267- 74.
 20. Conacher ID. Post-thoracotomy analgesia. *Anesthesiol Clin North America* 2001; 19 (3): 611- 25.
 21. Richardson J, Sabanathan S, Shah R. Post-thoracotomy spirometric lung function: the effect of analgesia. A review. *J Cardiovasc Surg (Torino)* 1999; 40 (3): 445- 56.
 22. Ochroch EA, Gottschalk A, Augustides J, Carson KA, Kent L, Malayaman N, et al. Long-term pain and activity during recovery from major thoracotomy using thoracic epidural analgesia. *Anesthesiology* 2002; 97 (5): 1234- 44.
 23. Tan CN, Guha A, Scawn ND, Pennefather SH, Russell GN. Optimal concentration of epidural fentanyl in bupivacaine 0.1% after thoracotomy. *Br J Anaesth* 2004; 92 (5): 670- 4. Epub 2004 Mar 19.
 24. Arif yegin. Early postoperative pain management after thoracic surgery, pre. and post op versus post op epidural analgesia: a randomized study. *European J of Cardio Thoracic Surg* 2003; 24: 420- 4.
 25. Antonia Macias. A Randomized double blind comparison of thoracic Epidural Ropivacaine, Rpivacaine, Ropivacaine/*Anest Analg* 2002; 950: 1344-50.
 26. Romer HC, Russell EN. A Survey of practice of thoracic epidural analgesia in the United Kingdom.
 27. Ong, Cliffk. S lirk, Philip. The Efficacy of preemptive analgesia for acute postoperative pain management. *A analysis Anesth Analgesia* 2005; 100 (3): 757-73.
 28. Della Rocca G, Coccia C, Pompei L, Costa MG, Pierconti F, Di Marco P, et al. Post-thoracotomy analgesia: epidural vs intravenous morphine continuous infusion. *Minerva Anesthesiol* 2002; 68 (9): 681- 93. English, Italian.
 29. Grant RP, Dolman JF, Harper JA, White SA, Parsons DG, Evans KG, et al. Patient-controlled lumbar epidural fentanyl compared with patient-controlled intravenous fentanyl for post-thoracotomy pain. *Can J Anaesth* 1992; 39 (3): 214- 9.
 30. Baxter AD, Laganiere S, Samson B, Stewart J, Hull K, Goernert L. A comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy analgesia. *Can J Anaesth* 1994; 41 (3): 184- 91.
 31. Miguel R, Hubbell D. Pain management and spirometry following thoracotomy: a prospective, randomized study of four techniques. *J Cardiothorac Vasc Anesth* 1993; 7 (5): 529- 34.
 32. Ozyalcin NS, Yucel A, Camlica H, Dereli N, Andersen OK, Arendt-Nielsen L. Effect of pre-emptive ketamine on sensory changes and postoperative pain after thoracotomy: comparison of epidural and intramuscular routes. *Br J Anaesth* 2004; 93 (3): 356- 61. Epub 2004 Jul 9.
 33. Noboisseau. Improvement of dynamic analgesia dose not decrease after thoracotomy. *BJA* 2001; 87 (4): 564-69.
 34. James MF, Heijke SA, Gordon PC. Intravenous tramadol versus epidural morphine for postthoracotomy pain relief: a placebo-controlled double-blind trial. *Anesth Analg* 1996; 83 (1): 87- 91.
 35. Senturk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalcin S, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* 2002; 94 (1): 11-5.

36. Bloch MB, Dyer RA, Heijke SA, James MF. Tramadol infusion for postthoracotomy pain relief: a placebo-controlled comparison with epidural morphine. *Anesth Analg* 2002; 94 (3): 523- 8.
37. Parramon F, Garcia Ch, Gambus P, Vilaplana J, Aragonés N, Villalonga A. [Postoperative patient-controlled analgesia is more effective with epidural methadone than with intravenous methadone in thoracic surgery]. *Rev Esp Anesthesiol Reanim* 2003; 50 (7): 326- 31.
38. Debrenceni G, Molnar Z, Szelig L, Molnar TF. Continuous epidural or intercostal analgesia following thoracotomy: a prospective randomized double-blind clinical trial. *Acta Anaesthesiol Scand* 2003; 47 (9): 1091- 5.
39. Bachmann, Menoga. Inter costal nerve block. *Eur J cardiothoracic surgery* 1993; 7 (10): 561-9.
40. Dauphin A, Lubanska-Hubert E, Young JE, Miller JD, Bennett WF, Fuller HD. Comparative study of continuous extrapleural intercostal nerve block and lumbar epidural morphine in post-thoracotomy pain. *Can J Surg* 1997; 40 (6): 431- 6.
41. Takamori S, Yoshida S, Hayashi A, Matsuo T, Mitsuoka M, Shirouzu K. Intraoperative intercostal nerve blockade for postthoracotomy pain. *Ann Thorac Surg* 2002; 74 (2): 338- 41.
42. Mitsuhata H, Kawakami T, Togashi H, Hirabayashi Y, Saitoh K, Fukuda H, et al. [The effects of continuous interpleural vs. epidural infusion for postoperative pain relief following thoracotomy]. *Masui* 1994; 43 (10): 1478- 85.
43. Brockmeier V, Moen H, Karlsson BR, Fjeld NB, Reiestad F, Steen PA. Intercostal or thoracic epidural analgesia for pain after thoracotomy. A double blind study. *Acta Anaesthesiol Scand* 1994; 38 (4): 317-21.
44. Miguel R, Hubbell D. Pain management and spirometry following thoracotomy: a prospective, randomized study of four techniques. *J Cardiothorac Vasc Anesth* 1993; 7 (5): 529- 34.
45. Gaeta RR, Macario A, Brodsky JB, Brock-Utne JG, Mark JB. Pain outcomes after thoracotomy: lumbar epidural hydromorphone versus intrapleural bupivacaine. *J Cardiothorac Vasc Anesth* 1995; 9 (5): 534-7.
46. Mehta Y, Swaminathan M, Mishra Y, Trehan N. A comparative evaluation of intrapleural and thoracic epidural analgesia for postoperative pain relief after minimally invasive direct coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 1998; 12 (2): 162- 5.
47. Demian AD, Wahba AM, Atia EM, Hussein SH. Bilateral interpleural versus lumbar epidural bupivacaine-morphine analgesia for upper abdominal surgery. *Middle East J Anesthesiol* 2003; 17 (3): 347- 58.
48. Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. *Br J Anaesth* 1999; 83 (3): 387- 92.
49. David N. Bisrnston. Continuous Paravertebral extrapleural infusion for post thoracotomy pain management surgery: 1999; 83: 387-92.
50. Santhos Kumar T. Comparative evaluation of thoracic epidural vs thoracic paravertebral block for post thoracotomy pain relief with 0.25% Bupivacaine. *Indian J Anesth* 2003; 47 (4): 269-74.
51. Richardson J, Sabanathan S, Shah R. Post-thoracotomy spirometric lung function: the effect of analgesia. A review. *J Cardiovasc Surg (Torino)* 1999; 40 (3): 445- 56.
52. D. Yi Jun. comparison of the efficacy of cryo and patient controlled apidural analgesia after thoracotomy. *Xue Bao* 2005 Apr, 25 (4): 469-70, 443.
53. Yang MK, Cho CH, Kim YC. The effects of cryoanalgesia combined with thoracic epidural analgesia in patients undergoing thoracotomy. *Anaesthesia* 2004; 59 (11): 1073- 7.
54. Moorjani N, Zhao F, Tian Y, Liang C, Kaluba J, Maiwand MO. Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves: a human prospective randomized trial and a histological study. *Eur J Cardiothorac Surg* 2001; 20 (3): 502- 7.
55. Brichon PY, Pison C, Chaffanjon P, Fayot P, Buchberger M, Neron L, et al. Comparison of epidural analgesia and cryoanalgesia in thoracic surgery. *Eur J Cardiothorac Surg* 1994; 8 (9): 482- 6.

56. Miguel R, Hubbell D. Pain management and spirometry following thoracotomy: a prospective, randomized study of four techniques. *J Cardiothorac Vasc Anesth* 1993; 7 (5): 529- 34.
57. Berrisford RG, Sabanathan SS. Cryoanalgesia for postthoracotomy pain. *Ann Thorac Surg* 1990; 49 (3): 509-10.
58. Joucken K, Michel L, Schoevaerdt JC, Mayne A, Randour P. Cryoanalgesia for post-thoracotomy pain relief. *Acta Anaesthesiol Belg* 1987; 38 (2): 179- 83.
59. Roxburgh JC, Markland CG, Ross BA, Kerr WF. Role of cryoanalgesia in the control of pain after thoracotomy. *Thorax* 1987; 42 (4): 292- 5.