КЛИНИЧКИ ИСТРАЖУВАЊА

ЕПИДУРАЛНА АНАЛГЕЗИЈА ПРИ НЕСНОСНА КАНЦЕРСКА БОЛКА - СТАРА ПРИКАЗНА СО УПОТРЕБА ДО ДЕНЕС

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Извадок

Канцерската болка е неиздржлива хронична јака болка која влијае врз квалитетот на животот на болните и претставува тежок здравствен, социјален и семеен проблем во многу земји. Светската здравствена организација (СЗО) предлага низа методи за нејзино сузбивање Епидуралната аналгезија со опиоиди е еден од предложените методи. Цел на трудот е да се утврдат ефектите на морфин, фентанил и буторфанол, употребени за епидурална аналгезија при неиздржлива болка, како и да се прокоментираат искуствата од петтодишен период со осврт кон актуелноста на методот денес. Материјал и методи: ретроспективна лонгитудинална опсервациска студија, спроведена на Универзитетската клиника за анестезија, реанимација и интензивно лекување, КАРИЛ, Скопје, Република Северна Македонија, во периодот помеѓу 2005-2010, со осврт на 2017-2018. Во студијата беа вклучени 116 болни кои страдаа од несносна канцерска болка, додека, пак, не беа вклучени болните со инфективни и метастатски процеси во 'рбетот, алергија на опиоиди, психолошки проблеми и јазична бариера. Непосредно пред третманот, кај болните се евалуираше степенот на болката и тие беа рандомизирано одредени за аналгезија со еден од трите опиоида, кои се аплицираа преку епидурален катетер поставен на височина Th8-10 или L2-3. Резултати: Со студијата се потврди дека степенот на болка пред третманот не се разликуваше меѓу трите групи (p>0,05). Се постигна сигнификантна аналгезија по 15 минути во групата со буторфанол, по 20 минути со фентанил и по 30 минути со морфин (p<005). Времетраењето на аналгезијата буторфанол vs. фентанил vs. морфин беше 6 часа vs. 8часа vs. 24 часа. Со морфинот се постигна најдолга аналгезија (p<0,05). Заради зголемувањето на прагот на болката, со тек на време беше неопходно да се зголеми дозата на опиоидот. Најчесто реферирани несакани ефекти беа: чешање, констипација, уринарна ретенција и диспнеја, а отсуствуваа изјави за лошење и повраќање. Заклучок: Со оваа студија се потврди дека епидуралната аналгезија со опиоиди претставува ефикасен и сигурен метод за сузбивање на неиздржлива болка. Покрај другите алтернативи за третирање на канцерската болка, епидуралната аналгезија со опиоиди сеуште зазема еминентно место, а нејзината употреба е предизвик за професионалците.

CLINICAL SCIENCE

EPIDURAL ANALGESIA FOR INTRACTABLE CANCER PAIN - AN OLD STORY USED UNTIL NOW

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Abstract

Intractable cancer pain is a chronic severe pain, affecting patient's quality of life and presents aheavy health, social and family problem in many countries. Different methods for pain relief are proposed by the WHO. Epidural analgesia with opioids is one of the proposed methods. Aim of the study was to determine the effects of morphine, fentanyl and butorphanol used for epidural analgesia in intractable pain and to comment our experiences over a five-year-period, with regard to its actuality nowadays. Material and methods: Retrospective longitudinal observational study was carried at the University Clinic for Anesthesiology, Reanimation and Intensive Care in Skopje, Macedonia, between 2005-2010 and evaluated in 2017-2018. A total of 116 patients suffering from intractable pain were enrolled in the study. Exclusion criteria were: infective and metastatic processes in the spine, allergy to opioids, psychological problems and language barrier. After the pretreatment evaluation of the pain, patients were randomly assigned to receive three different opioids through epidural catheter placed from Th8-10 or L2-3. Results: There were no differences in pretreatment pain scores between the three groups (p>0.05). A significant onset of analgesia after 15 minutes was found for butorphanol, 20 minutes for fentanyl and 30 minutes for morphine group (p<0.05). The duration of the pain relief of butorphanol vs. fentanyl vs. morphine was 6h vs. 8h vs. 24 hours respectively. Morphine had the longest duration of pain relief (p<0.05). Because of an increase in the pain threshold, the need of an increase of opioid doses was necessary. The most often patient's reports of side effects were: itching, constipation, urine retention and bradypnea and there were no reports of nausea and vomiting. Conclusions: It was concluded that epidural analgesia with opioids is an effective and safe method for suppression of intractable pain. In spite of the other alternatives in treatment of cancer pain, epidural analgesia with opioids still has an eminent place and its use is a challenge for professionals.

Introduction

Intractable cancer pain is a chronic severe pain, persisting at all times and affecting patient's quality of life[1]. The patients with chronic cancer pain present heavy health, social and family problem in our and other countries. Pain management of this group of patients has human and medical dimensions[2,3]. For this reason, the World Health Organization (WHO) proposed "the analgesic ladder method" for pain relief of this group of patients.

The essences of this therapy are to give analgesics consecutively in order (ladders). The first ladder is the use of non opioids, followed by mild opioids and at the end (the last ladder) are strong opioids, until the patient is free of pain. For better pain relief drugs should be given "by the clock" (exact timing), with the use of "adjuvants" if it is necessary[4,5].

In such circumstances, to relieve intractable pain, the use of epidural analgesia with opioid is one of the preferable methods. The application of a minimal dose of opioids in the epidural space produces prolonged segmental analgesia without motor and sympathetic blockade[6]. The analgesic effect is produced by acting on receptors located on neuronal cell membranes. The blocking effect of opioids in the spinal cord is on the level of "supstantia gelatinoza" where the opioids receptors are located. The major presynaptic action of opioids in the nervous system is to inhibit the release of neurotransmitters[7].

This method for pain relief (epidural analgesia) has been used at our Clinic since 1985. In the very beginning it was used as a method for treatment of postoperative pain, but very soon it became a superb method for pain relief in intractable pain of patients who suffered from chronic cancer pain.

The aim of this study was to make a retrospective analysis of the effects of this old method of pain relief and to give a summary of our experience during a five-year-period, with regard to its actuality nowadays.

Material and methods

This study was conducted between 2005-2010, at the University Clinic for Anesthesiology in Skopje R. Macedonia. It was a part of the project "Development of the patronage service for pain relief'", in collaboration with the Hospice "Sue Rider" in Skopje. The design of the study was approved by the Ethics Committee of our Clinic.

The study group consisted of 116 patients suffering from intractable pain, which during this period required interventions in our outpatient clinic, where they were treated with epidural application of opioids.

The selection of patients was based according to the intensity and location of the pain, the findings of the spinal cord and the acceptance of the patient to be treated with this method. The pain intensity at rest >70 mm on the Visual Analogue Scale (VAS), which lasted for more than 3 months, resistant to conventional therapy, was accepted as an intractable pain8. Patients with metastatic and infective processes in the spine, allergy to opioids, psychological problems and language barrier were excluded from the study. A written signed consent was obtained from all patients included in this study.

All patients were interviewed for main complaints, medical history and pain history. The information about diagnostic findings, results, analyses of laboratory tests and the screens were checked. A complete physical examination of the patients was performed

and data about the previous analgesic interventions and drugs were noted.

All enrolled patients (n=116) were informed about the procedure, educated about self-injection, the use of 100mm Visual Analogue Scale (VAS) and how to fill in the questionnaire specially designed for this study. The scheme of analgesic treatment was explained to all patients as well.

The procedure started with an evaluation of the pain, according to the Visual Analogue Scale (VAS) and the opening of an intravenous (IV) line. All patients received IV infusion of 500 mL of lactated Ringer's solution prior to application of the epidural catheter (in sterile conditions). Depending on the health state of the patients, epidural procedure was performed in a sitting or lying position. The injection was done using a 16 G Tuohy needle through which an appropriate catheter was inserted. Depending on the origin of the pain, the epidural punctures were at the level of Th8-10 or L2-3. The catheter was tunneled subcutaneously on the upper direction with the aim to enable patient's comfort and to avoid superinfection9. The test dose of 3ml 0.5% bupivacaine was inserted and the sensory was checked; after a negative response at 5 min, without loss of sensation, an application of opioid was performed.

The starting dose for epidural application was as follows: morphine 3mg with 8 ml diluents, fentanyl 30 μgr with 10 ml diluents or 1 mg methadone with 9 ml diluents.

After the daily evaluation of the pain, the doses were adjusted with the analgesic needs of the patients, and the addition doses of the epidural opioid or oral analgesic were prescribed.

The level of pain, the onset and the duration of the pain relief, the need for additional doses of analgesics during a 4-week-period and the side effects were noted in the questionnaire.

The numerical data in the study were statistically elaborated by using mean, standard deviation and the paired Student's t-test. Mann Whitney U test was used as additional statistics. A p value of < 0.05 was considered to indicate a statistical significance.

Results

The basic demographics of the included patients are presented in Table 1.

Table 1. Demographic distribution of patients (M±SD)

Period of time	Number of patients		Age	Weight
	Male	Female		Kg/
2005-2006	3	2	57±2	64±7
2006-2007	19*	2	62±10	69±5
2007-2008	15*	13*	64±7	58±11
2008-2009	22*	9	61±3	49±8
2009-2010	30*	3	63±7	55±9
Total	87	29		
5 years	**116 patients**		**61±4**	**59±5**

* $p<0.05$

During the five-year-period, 116 patients with cancer pain were treated with regional analgesia through epidural application of opioids. The distribution by sex was 87 males and 29 females, hence, the predomination of male patients was obvious. A small group of patients was included in the first year, but in the following years this number was statistically significantly increased ($p<0.05$).

Table 2 presents the distribution of the patients according to the diagnosis and the level of the epidural puncture.

Table 2. Diagnosis and level of epidural puncture (n=116)

Period of time	Number of patients	Age
Low abdomen: • Ca rectum • Ca colon • Ca urinary bladder	90 (77.58%)*	Th 10-L1 Th9-L1 L2-L4
Inoperative Ca of the lungs	14 (12.04%)	Th 8-10
Other locations	12 (10.34%)	L2-L3

* $p<0.05$

The main cause of the pain, in most of the treated patients, was the grade of the carcinoma after surgery, or an inoperable state of the carcinoma in the lower abdomen more often than in other locations (90 vs.26) ($p<0.05$).

According to 100 mm VAS, the pain was evaluated in pain scores. In Table 3 the results of the pain scores obtained on the first day of treatment are presented. The primary level of pain was checked, and after the application of the drugs, the onset and the duration of the pain relief were measured.

Table 3. First day pain evaluation and analgesic efficiency-VAS (M±SD)

Drug	Time t 0	15 min	30 min	6h	12h	18h	24h
Morphine 3mg (n=87)	80.7±7.3	39.19±9.4	18.3±4.8*	17.9±5*	18.4±5.1*	44±7.3	61.1±11.4
Fentanyl 30 µg (n=26)	81.8±7.4	34.1±5.6	22.4±4.1*	29.2±9.3	64.7±17.6		
Butorphanol 1mg (n=3)	79±2.9	26.3±5.3*	19±5.2*	50±10.8	72.3±2.0		
Difference	NS	*p< 0.05					

It was obvious that at time zero (t 0), the primary measured level of pain between the different drug groups was insignificant (p>0.05).

The onset of the pain relief started after 15 minutes with a peak effect reached after 30 minutes. A significant onset of analgesia after 15 minutes was found for butorphanol, 20 minutes for fentanyl and 30 minutes for morphine group (p<0.05). A significant positive analgesic effect after 30 minutes was established for morphine, fentanyl and butorphanol (p<0.05). The duration of analgesia lasted 4-6 hours for butorphanol, 8-10 hours for fentanyl and 18-24 hours for morphine (Table 4).

Table 4 presents the results over the four-week-period with the doses of medications given in the epidural space.

In the analyzed material, it was found that morphine was the favorable drug for most of the patients (75%), followed by fentanyl (26.5%) and butorphanol (2.5%). In this four-week-period the dose of morphine increased from 3 to 8 mg per day; a multiplication of the dose of fentanyl from one to two times per day was established and three to four times per day for butorphanol.

Table 4. Doses of epidural opioids used in the four-week-period

Drug	Patients	1st dose	2nd week	3rd week	4th week	Analgesia (h)
Morphine	87 (75%)	3 mg	5 mg	7 mg	8 mg	24 h
Fentanyl	26 (26.5%)	30 μg	2x 30 μg	2x 30 μg	2x 30 μg	≈10 h
Butorphanol	3 (2.5%)	1mg	3x	4x	4x	6.5h
Total	116 (100%)					
Bupivacaine 0.125%	13 (15%)					

As adjuvant, local anesthetic 0.125% bupivacaine was used in 15% of the patients.

According to the duration of the epidural treatment the doses of application of the drug were increased successively. The patients were educated for self-application of the medication in the epidural catheter.

In the first week of the treatment, the first dose was satisfactory for 89% of the treated patients with analgesia from 6-24 hours depending on the drug. After seven days of treatment, the first signs manifested that the threshold of the pain was increased, and consecutively the doses of the opioids were increased or exchanged by another drug.

In our series, in 78% of the treated patients with morphine, the dose of 3 mg epidural morphine was increased to 5 mg, in 10% the dose was increased to7 mg given in 24h; in 12% of patients the dose of morphine was 8mg/24 h or it was substituted by fentanyl or butorphanol.

The duration of the epidural treatment lasted from 30 to 60 days. The treatment was interrupted because of the development of complications or because of the end of the life.

Table 5. Side effects after epidural application of opioids (N/%)

Side effect	Morphine (n=87)	Fentanyl (n=26)	Butorphanol (n=3)
Bradipnea	4 (4.5%)*	0	0
Itching	85 (97.7%)	25(96.7%)	2
Urine retention	14(16%)	13(50%)*	/
Constipation	17(19.5%)	4 (15.38%)	/
Local infection	2(2.2%)	/	/
Nausea/vomiting	2(2.2%)	/	/
Drowsiness	/	/	/
Allergy	/	/	/

*p< 0.05

The most often seen side effect was itching, which was present in the three used opioids. Urinal retention was less present than expected, but most of the patients were with urine catheters. Also, constipation was present in small numbers, because it was prevented with the use of bupivacaine 0.1%. Two patients who developed local infection were shifted to other treatment and excluded from the study.

Discussion

Opioids are important drugs used in the pain relief management. The regional analgesia with opioids probably achieved the veritable point of the WHO's pain relief ladder suggestion for a "freedom in the treatment of cancer pain" [10, 11].

The fundamental discovery in1977 by Jaksh TL and Rudy TA that opioid receptors are located in substantia gelatinosa in dorsal corns of the spinal cord, announced a new era in the treatment of pain on segmental level[12, 13]. The small dose of opioids given in the epidural space has prompted analgesic reaction, without sedation, unwanted central sensory effects like drowsiness and euphoria. Morphine is a 'gold-standard' single-dose epidural opioid due to its analgesic efficacy and prolonged duration of action.

However, the risks of development of side effects like itching, nausea and vomiting, urinary retention, constipation and, the most important, respiratory depression are not excluded [14].

The retrospective critical analyses of the results obtained have shown that the method of epidural analgesia with opioids provided successful pain relief. The development of side effects was in the ranges of the anticipations. The effects of opioids on respiration were only with the development of bradipnea. Respiratory arrest was not perceived in this group. We speculate that the main reason for this was the use of small doses of narcotics, and secondly, the use of diluents as well as the intact durra insured by the pretreatment test dose.

Several authors studied the reasons for development of respiratory de-

pression after epidural administration[15-17]. Most of them agree that the migration of opioids in intrathecal space could be one of the possible reasons for incidents with respiratory depression[18,19]. First of all, the explanation was that opioids in the cerebrospinal fluid interac with opioid receptors in ventral medulla. Later studies have shown that the main places of activity are neurons of the pre-Bötzinger complex in the medulla as mediators of opioid-induced respiratory depression, where the expressing neurokinin-1 receptors are selectively inhibited by opioids [20]. Other authors have found that the development of respiratory depression is more specific for opioids agonists connected to mu-receptors, and its lipo-solubility. Therefore, according to the ASA guidelines, all participants in this study, prior to epidural treatment, were submitted to a serious identification for possible risk factors [21, 22].

We can conclude that in our series the number of treated patients was not high. We believed that it was due to the disbelief of some of the patients; for some of them the method was too aggressive, or they were scared, and some of the patients were not prepared for self-treatment. Additionally, general practitioners were not informed about the possibility for epidural treatment of the pain.

The number of the treated patients from year to year has increased significantly ($p<0.05$). The efficacy of the pain relief treatment has been successful in 99% of the patients. The use of VAS for evaluation of the pain may be not the appropriate method, but it is simple and accurate and is very easy and well accepted by the patients [23-26].

The main findings are that good analgesic effects are related to the close relationship of the therapist and the patient and achieved confidence between them.

The main benefits of the epiduraly applied opioids are good analgesia, improved quality of life and physical function. The therapy must be balanced against the risks of side effects[27, 28].

This five-year experience showed that the method of epidural analgesia with opioids was and still is an alternative among the methods for treatment of the intractable pain inpatients with carcinoma.

This method was very popular in the 1990's. The development of less aggressive methods for pain relief, such as fentanyl patch, patient control analgesia (PCA), the prescriptions of oral opioids and other strong analgesics from non-opioids origin, suppressed epidural analgesia as the main pain relief method [29]. The establishment of medical cannabis as an alternative therapy in cancer pain opens a new way in the management of intractable pain.

Today, epidural analgesia has an ultimate place in pre-emptive analgesia, during regional and general anesthesia and in the variety of "opioid spearing techniques" that can reduce the postoperative pain and shorten the recovery period after surgery.

This was documented in several trials and it was concluded that regional techniques used as pre-emptive therapy, before the pain appears, lead to a decreased need of opioids for analgesia [30].

The main side effect that discredited the use of epidural analgesia with opioids was the development of constipation. Continual assessment of the efficacy and tolerance of the drug is essential. Liu SS. with his team in 1995 compared 4 studies about the epidural bupivacaine with epidural opioid, and 3 of these studies demonstrated a significant reduction in the duration of postoperative ileus in the epidural bupivacaine group compared tothe epidural opioid group[31,32]. This was the reason for using epidural bupivacaine (0.125%) in small doses which showed successful results as adjuvant [33].

Today, there are different analgesic modalities as "opioid spearing techniques" which are used often and have minimal impairment of GI function.

The concept of a multimodal analgesic program in which pain relief is a key factor is a major task for the future. The pain management strategy in multimodal protocols is using epidural analgesia, ketamine, acetaminophen, gabapentin and COX-inhibitors. These concepts ensure that the "era" of epidural analgesia is still actual for pain management in patients with intractable cancer pain [34].

Conclusion

It can be concluded that the forgotten method of epidural analgesia with opioids for the treatment of cancer pain should be revised. It seems that it is still the most efficient method to suppress the intractable pain. It is with a prompt and long duration analgesic effect. Epidural analgesia with opioids is an effective and safe method for suppression of intractable pain. In addition to the other alternatives in treatment of cancer pain, epidural analgesia with opioids still has an eminent place and its use is a challenge for professionals.

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