Studii şi Cercetări	Mai 2021	Biologie	30/2	77-80	Universitatea"Vasile Alecsandri" din Bacău

OPTIMIZED CHRONIC PAIN CONTROLL BY IMPLANTED PUMPS INTRATHECAL

Jean Ciurea, Felix Brehar, Alin Rasina, Ana Gheorghiu, Tatiana Ciurea

Key words: *pain management, analgesia, intrathecal therapy,implantable pump, targeted drug delivery, visual analogue scale (VAS)*

INTRODUCTION

Neuromodulation is based on electrochemical nature of the nervous system. Implantable medical devices open a new era in therapy. They are based on electricity and molecules of medication. Electrical neuromodulation canblock pain signals as they travel from periphery to the brain where pain is perceived, analyzed, and induce a reaction. On the other side, targeted drug delivery (TDD) is based on its chemical nature. Specific molecules like opioids act directly into the intrathecal space, on pain receptors in the spine more efficient compared to oral or circulatory system.

Targeted Drug Delivery (TDD) is a safe, proven, and effective to control chronic pain.Doses are lower than in oral medication. Fewer side effects are reported in TTD. (*Hamza M et al. 2012; Smith TJ et al. 2002).*

The system is based on a fully implanted programmable pump and intrathecal catheter designed to deliver pain-relieving medications to the spinal cord pain receptors. *(Onofrio BM, et al. 1981)*. It was launched in the 1980's and has been developed continuously since.

The benefit of injecting opioids in cerebrospinal fluid are associated with reduced drug effects on the brain, mainly addiction, but with much lower doses of opioid than the doses used intravenously or arally, the analgesic effect is amplified. *(Grider JS et al. 2016; Hamza M, Doleys D, Wells M et al. 2012).*

PATIENTS AND METHOD

Several of 12 patients were selected from the larger total of implanted patients as this study focused on pain. The others presented different therapy indications. There were 3 women and 9 men. There is only one patient with malignant pain due to a astrocytoma on the spinal cord resected in unother surgical department. The age ranged between 29 to 75 years old (mean 47 years). All were tested and implanted.

Patient selection is the most important step to get a good result.

Malignant pain in patients where survival is estimated to more then 3 -6 months may benefit of this therapy. Patients with cancer experience chronic pain that can often intolerable. Their survival extended in the recent years so exists an increase necessity to manage cancer pain. Chronic pain usually lasts longer than three to six months. (*Treede, Rolf-Detlef et al. 2015; Dahlhamer J et al. 2016).*

Before starting the implantation procedure which consists of testing and surgery, the patient or the legal representative gives his consent, signs a statement starting that they have been fully informed.

A multiple specialist's team must decide the opportunity of pump implantation. The neurologist and psychiatrist examinations are mandatory and in case of malignant pain, the oncologist.

Psychiatric screening is performed as part of the patient selection process for identification of psychiatric disorders known higher in patients with chronic pain relative to the general population. Psychiatric associated conditions mayinfluence the success of the procedure. Patients with suicidal depression, schizophrenia with active psychotic behavior, active suicidal or homicidal tendencies, or active substance abuse must be excluded from surgery.

Test of opioid intrathecal effects on pain.

A spinal catheter is introduced by a Touhy needle in lumbar subdural space between the last two vertebrae. The cerebrospinal fluid drops are obtained at external end of the catheter proving a possibility to inject a prescribed amount of medication by a calibrated electronic continuous infusion syringe. Due to respiratory depression induced by opioids, the patient is closely monitored during and after the test. This can take from hours to days

The definition of successful pain relief is ≥50% reduction in VAS.(*Anderson VC et al. 2003).*

If the test is positive, the catheter is removed, and patient prepared for surgery not earlier than 24 hours due to the risk of infectious complications (meningitis).

The SynchroMedTM Intrathecal Drug Delivery system, inject directly to the fluid around the spinal cord. It is an alternative to oral opioids for patients. Pain relief is accomplished at a fraction of

the oral dose. Side effects are lower. The objective is reduced or eliminate the use of oral opioids.

The Medtronic pain pump also allows for full-body MRI scans when following the product labeling. (*Smith TJ et al. 2002; Deer T et al. 2004; Atli A et al. 2010; Hatheway JA et al. 2015; Grider JS et al. 2016).*

Surgical technique

The patient is put on general anesthesia and placed on the right side. An incision is done in paraumbilical region, and the pump pocket is prepared in subcutaneous fatty tissue keeping in mind that if it is too deep, the refilling needle does not reach the pump and too superficial can cause trophic skin lesions. Hemostasis is essential to avoid complications. The spinal catheter is introduced in subdural space, passed thru a tunnel under the skin and connected to the pump.The pump is filled with prescribed concentration of drug and the flux is fixed by a programmer thru the skin. It is recommended to start with a small amount of morphine and to increase it progressively.*(Deer TR et al. 2017).*

The refilling is a key factor in maintaining a good function of the pump and avoid complications, mainly infection. A meningitis can compromise pump. Fast injection can block the pump. A human error in programing the pump can be fatal for the patients **(Fig.1).**

A clean surgery, good hemostasis and careful follow up of protocol is the way to avoid complications. Postop monitoring is focusing on neurological signs, respiratory signs, and woundhealing.

Back pain, paresthesia, motor deficits must be identified, and their causes established. A hematoma compressing the spine must be evacuated immediately.A respiratory depression needs a active breath support by assisted ventilation and lumbar puncture in order to remove opioid molecules responsible for depression.

RESULTS AND DISCUTIONS

The visual analog scale (VAS) is a subjective evaluation of pain. The person is asked to indicate his/her perceived pain intensity indicating a mark from 0, which means no pain, to 10 which means the highest possible level of pain. *(Myles, Paul S. et al. 1999).*

All patients improved their pain perception from severe before surgery (> 5 on VAS) to moderate (< 3 on VAS) at doses of less than 1.0 mg/day.

All patients reported, when admitted for pump refill, they were less exhausted and depressed being more active, and able to return to their jobs and hobby.

Our policy was to maintain opioids prescription as low as possible. When necessary, oral pregabalin(Lyrica) 300 mg twice a day was successfully associated, generally after two years after implantation. Meanwhile, 92% of patients reduced their oral opioids and 6% stopped it.

Patients did not develop secondary effects like sleepiness, nausea, and constipation.

One patient accused pump site pain, but no local signs of inflammation, intolerance of infection.No serious adverse events were recorded in our patients.

Pump function is evaluated in most cases at five years.A close contact with the patients is important since the prescribing physician must adapt to their needs.With the use of implantable systems for chronic pain, studies have focused on monotherapy, the use of a small dose of analgesic applied intrathecally with the elimination of a systemic ones. Microdoses of morphine (doses less 1.0 mg/day) prescribed in the clinic and the lack of side effects recommend this therapy for a long time. *(Wilkes DM et al. 2017).*

Implantable pumps can be programmed to provide a certain amount of analgesic and give patients with pain the opportunity to control their analgesia. Patients' access to the personal programmer is made with the doctor's consent. The scheduling parameters are set to a constant daily dose and the dose delivery time can be changed by the patient using the scheduler. The risk of overdose should be avoided and increasing doses of morphine may lead to decreased pain control. (Fig. 2).

If a system ceases to function, after reimplanting the same dose can be fatal. The recommendation for implanters is "start low, go slow".*(Coffey RJ et al. 2009).*

When trying to lower or eliminate opioids it is important to start a replacement therapy, otherwise the patient faces discomfort and severe pain.*(Dowell D et al. 2019).*

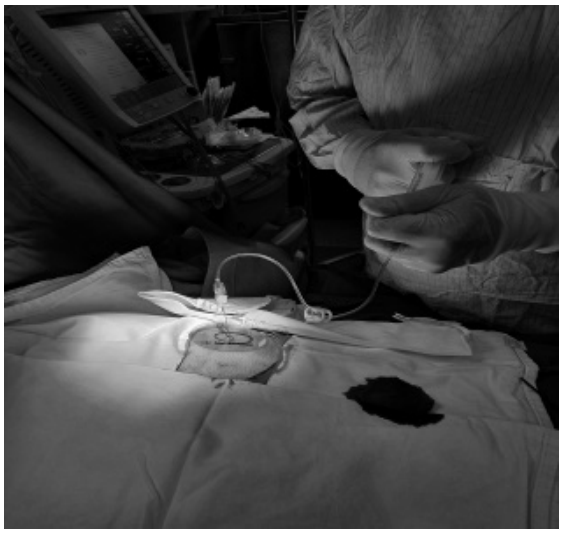

Fig. 1. Pump refill in Operating Theater

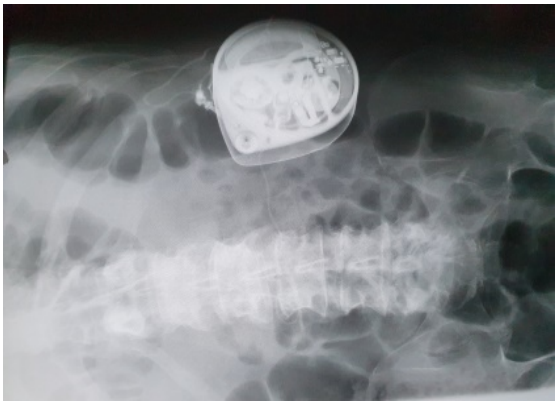

Figure 2. Radiological control (Chronic malignant pain)

Pump malfunctions, including both mechanical failure of the pump or battery and pump rotor malfunction, are rare and we did not report no case.Mispositioning of pumps is due to a poor fixation or the patient is playing with it. If the refilling side is turned, then a surgical procedure for reorientation is mandatory. Bleeding and infection are major complication of this procedure and can either occur at the site of the pump, at lumbar wound, or as meningitis.

A pharmacologic complicationis represented by catheter-tip granuloma which can compromise the whole procedure. It is documented by neuroimager, magnetic resonance imaging only for Synchromed II pump.

Refill complications avoidance impose a sterile procedure in operating theater order to prevent infection.

Intrathecal ziconotide is a promising replacement of opioids and hopefully available for us soon.

CONCLUSIONS

Intrathecal therapy has been demonstrated to be highly effective in treating chronic pain.

The success depends on patient selection excluding those with risk of bleeding, opioid abuse, psychological comorbidities, and infection. Medications utilized must be adapted to patient needs. Close connection and understanding patients is time consuming and must be performed by trained personal. Suspicion for different complications and adverse events, is mandatory.

This procedure proved high effective, and safe but it can be optimized with prudent and judicious understanding all data in practice management.

ABSTRACT

Intrathecal therapy is accepted as an efficient therapy for chronic pain, both malignant and non-malignant. Infusion pumps produced by Medtronic were implanted in Functional Neurosurgery Dept. of “Bagdasar-Arseni” Hospital in Romania. Several of 12 patients were selected from the larger total of implanted patients as this study focused on pain. The others presented different therapy indications. The results are in range with published papers in this field. The standardized protocol was implemented successfully and improved by our team as presented in this paper.

REFERENCES

1. ANDERSON VC, BURCHIEL KJ, COOKE B. A prospective, randomized trial of intrathecal injection vs epidural infusion in the selection of patients for continuous intrathecal opioid therapy. *Neuromodulation.* 2003; *6*(3):142–152.
2. ATLI A, THEODORE BR, TURK DC, LOESER JD. Intrathecal opioid therapy for chronic nonmalignant pain: a retrospective cohort study with 3-year follow-up. Pain Med. 2010;11(7):1010-1016.
3. BLACKSHEAR PJ, ROHDE TD, PROSL F, BUCHWALD H; The implantable infusion pump: a new concept in drug delivery. Medical Progress Through Technology, 01 Nov 1979,6(4):149-161.
4. BOHM S, OLTHUIS W, BERGVELD P. Anintegrated micromachined electrochemical pump and dosing system. Biomed Microdevices. 1999;1:121–130.
5. COFFEY RJ, OWENS ML, BROSTE SK et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. Anesthesiology 2009;111:881–891. https://doi.org/10.1097/ALN.0b013e3181b64ab8
6. DAHLHAMER J, LUCAS J, ZELAYA C, NAHIN R, MACKEY S, DEBAR L, KERNS R, VON KORFF M, PORTER L, HELMICK C. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018 Sep 14;67 (36): 1001-1006. doi: 10.15585/mmwr.mm6736a2. PMID: 30212442; PMCID: PMC6146950.
7. DASH AK, CUDWORTH GC., 2nd Therapeuticapplications of implantable drug deliverysystems. J PharmacolToxicolMethods. 1998;40:1–12.
8. DEER T, CHAPPLE I, CLASSEN A, et al. Intrathecal drug delivery for treatment of chronic low back pain: report from the National Outcomes Registry for Low Back Pain. Pain Med. 2004;5(1): 6-13.
9. DEER T, KRAMES ES, et al. HASSENBUSCHS, et al. 2007. Polyanalgesic Consensus Conference 2007: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an

Interdisciplinary Expert Panel. *Neuromodulation*, 10:300–28.
10. DEER TR, POPE JE, HAYEK SM et al. The Polyanalgesic consensus conference (PACC): recommendations on Intrathecal drug infusion systems best practices and guidelines [published correction appears in Neuromodulation. 2017 Jun; 20 (4): 405-406]. Neuromodulation. 2017;20:96–132. *https://doi.org/10.1111/ner.12538*.).
11. DEO S, MOSCHOU E, PETEU S,EISENHARDT P, BACHAS L, MADOU M, DAUNERT S. Responsive drug delivery systems. Analytical Chemistry. 2003;75:207A–213A.
12. DOWELL D, COMPTON WM, GIROIR BP. Patient-centered reduction or discontinuation of long-term opioid analgesics: the HHS guide for clinicians. JAMA. 2019;322: 1855–1856. https://doi.org/10.1001/jama.2019.16409. 27. FDA Drug Safety Communication. https://www.fda.gov/media/122935/download
13. DOWELL D, HAEGERICH T, CHOU R. No shortcuts to safer opioid prescribing. N Engl J Med 2019;380:2285–2287.
14. EVANS AT, PARK JM, CHIRAVURI S, GIANCHANDANI YB. A low power, microvalve regulated architecture for drug delivery systems. Biomedical Microdevices. 2010;12:159–168. *https://doi.org/10.1056/NEJMp1904190*.).
15. GRIDER JS, ETSCHEIDT MA, HARNED ME et al. Trialing and maintenance dosing using a low-dose intrathecal opioid method for chronic nonmalignant pain: a prospective 36-month study. Neuromodulation 2016;19:206–219. https://doi.org/10.1111/ner.12352.
16. HAMZA M, DOLEYS D, WELLS M et al. Prospective study of 3-year follow-up of lowdose intrathecal opioids in the management of chronic nonmalignant pain. Pain Med 2012;13:1304–1313. https://doi.org/10.1111/j.1526-4637.2012.01451).
17. HARBAUGH RE: Intracerebroventricular bethanechol chloride administration in Alzheimer's disease. Presented at the New York Academy of Sciences, New York, June 13, 1987.
18. HARNEY D, VICTOR R. Traumatic syrinx after implantation of an intrathecal catheter. Reg Anesth Pain Med. 2004;29:606–9.
19. HATHEWAY JA, CARAWAY D, DAVID G, et al. Oral opioid elimination after implantation of an intrathecal drug delivery system significantly reduced health-care expenditures. Neuromodulation : journal of the International Neuromodulation Society. 2015;18(3):207-213.
20. MYLES, PAUL S. MBBS, MPH, MD, FFARCSI, FANZCA; Troedel, Sally MBBS; Boquest, Michael MBBS; Reeves, Mark MBBS The Pain Visual Analog Scale: Is It Linear or Nonlinear?, Anesthesia & Analgesia: December 1999 - Volume 89 - Issue 6 - p 1517doi: 10.1213/00000539-199912000-00038.
21. ONOFRIO BM, YAKSH TL, ARNOLD PG. Continuous low-dose intrathecal morphine administration in the treatment of chronic pain of malignant origin. Mayo Clin Proc 1981;56:516–520.
22. PAICE JA, PENN RD, SHOTT S. Intraspinalmorphine for chronic pain: a retrospective, multicenter study. J Pain SymptomManage. 1996;11:71–80.
23. POMM HA, TENZER P. Perspectives onchronic pain. Abstract 277. Program andabstracts of the American Academy of FamilyPhysicians Annual Scientific Assembly;September 28–October 2, 2005; San Francisco,Calif.
24. PRAUSNITZ MR. Microneedles for transdermaldrug delivery. Advanced Drug Delivery Reviews. 2004;56:581–587.
25. REYNAERTS D, PEIRS J, VANBRUSSEL H.An implantable drug-delivery system based onshape memory alloy micro-actuation. Sensorsand Actuators a-Physical. 1997;61:455–462.
26. SEBASTIANO MERCADANTE MD, Neoplasm-Induced Pain in Neurobiology of Disease, 2007.
27. SMITH TJ, STAATS PS, DEER T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drugrelated toxicity, and survival. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2002;20(19):4040-4049.
28. TREEDE, ROLF-DETLEF et al. "A classification of chronic pain for ICD-11." Pain vol. 156,6 (2015): 1003-1007. doi:10.1097/j.pain.
29. WILKES DM, Orillosa SJ, Hustak EC et al. Efficacy, safety, and feasibility of in community-based clinics. Pain Med 2017;0:1–8. https://doi.org/10.1093/pm/pnx132.

AUTHORS' ADDRESS

CIUREA JEAN, BREHAR FELIX, RASINA ALIN, GHEORGHIU ANA, CIUREA TATIANA - Functional Neurosurgery Department of "Bagdasar-Arseni" Hospital in Bucharest, Highway Berceni no. 12, Sector 4, București, Romania, e-mail: ciurea_t@yahoo.com