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Systematic Literature Search for MSCR Thesis: Intrathecal Pain Pumps for the Treatment of Neuropathic Pain

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MeSH Terms

Drug Delivery Systems; Neuralgia; Infusion Pumps, Implantable; Analgesics, Opioid; Pain /drug therapy

Introduction

Existing therapies for chronic neuropathic pain, which affects 10% of the United States population (1), leave much to be desired. Most patients suffering from this condition will not obtain sufficient pain relief from current recommended pharmacological therapy (2, 3). Current treatment approaches typically rely heavily upon oral opioids, which lead to problems with drug tolerance as well as hyperalgesia, and contribute to risk of drug abuse and potentially death from overdose. An alternative to oral opioid treatment is an intrathecal "pain pump," which provides locally-administered medication with automated control, decreasing the potential for abuse. While generally considered to be beneficial for cancer pain, pain pumps are used inconsistently for neuropathic pain conditions. Perhaps because of this, their role in the treatment of chronic neuropathic pain is poorly studied.

The etiology of chronic neuropathic pain differs from that of typical pain produced by tissue injury (nociceptive pain). Any pathologic process that disrupts normal pain projection after an initial lesion to the nervous system can cause neuropathic pain. In this context, microglia, the non-neuronal cells of the central nervous system, contribute to neuropathic-pain processing by releasing classic immune signals. These signals induce pro-inflammatory responses with pathological effects such as neuronal hyperexcitability (and therefore hyperalgesia), neurotoxicity, and chronic inflammation (4). Short-term perineural inflammatory activity is likely to be an adaptive response to acute nerve injury. When persistent, it unfortunately may become maladaptive and paradoxically result in severe, "burning" type pain that persists even in the absence of any overt lesion. Despite expanding knowledge of the distinct and complex

mechanisms underlying chronic neuropathic pain over several decades (4), all current first-line drugs for neuropathic pain target neurons.

Opioids are one such neuron-targeted class of drugs commonly used to treat neuropathic pain. Drugs of this class are quite effective at treating nociceptive pain. They are traditionally known to bind mu opioid receptors in the substantia gelatinosa in the dorsal horn of the spinal cord. Recently it has been discovered that opioids also directly activate supporting neuronal cells (glia), which in turn induce the release of neuroexcitatory pro-inflammatory cytokines that oppose the analgesic effects of opioids(4). This action causes opioids to counter their own productivity. This exacerbation of the underlying mechanisms of chronic pain ultimately makes opioids a particularly poor choice to treat a condition already known to have a strong immune signaling component.

We have seen a nearly fourfold increase in the use of prescribed opioids(5) for the treatment of pain coinciding with the increase in opioid overdose deaths(6) since the late 1990's when the Model Guidelines for the Use of Controlled Substances for the Treatment of Pain (7) were adopted by the Federation of State Medical Boards. While these guidelines were initiated by a justified concern that pain was being undertreated, overdose deaths due to opioids now far outweigh those due to illicit drugs. In this context of the public health crisis due to the prescription of oral opioids, we ask if there is evidence that delivering opioids via the secure, non-tamperable intrathecal pain pump, in combination with other synergistic medications will show improved pain scores and reduced side effects in patients with chronic neuropathic pain.

We evaluated the relative effectiveness of combination therapy that includes intrathecal pain pumps as compared to oral opioid treatment alone via a retrospective analysis of electronic medical records to compare analgesic efficacy as measured by pain scores in neuropathic pain patients. As a secondary outcome, we also analyzed whether side effects occur significantly less frequently in neuropathic pain patients treated with combination therapy via intrathecal pumps compared to those treated with oral opioid medications.

Research Question

We sought to determine if delivering opioids via the secure, non-tamperable intrathecal pain pump, in combination with other synergistic medications, would show improved pain scores and reduced side effects in patients with chronic neuropathic pain.

Replicable Search Strategy

For the literature search process for this study I queried PubMed using the MeSH database.

PubMed Search

Our PubMed search strategy involved the MeSH database in PubMed. The search to retrieve evidence for the use of intrathecal pain pumps for the treatment of neuropathic pain was thought of in two frameworks: the effect of pumps delivering different kind of medications or combination therapy intrathecally for neuropathic pain and the effect of opioids delivered intrathecally in general. The MeSH database in PubMed was accessed at http://www.ncbi.nlm.nih.gov/mesh. A new search was started on the MeSH homepage by entering "neuralgia" into the search bar in the MeSH database followed by the enter key. 15 types or descriptors of neuralgia appear under search results. The first one, "neuralgia" was selected as the most relevant search term to describe neuropathic pain.

While clinicians commonly refer to "intrathecal pumps," "pain pumps," or "intrathecal continuous catheters" these devices were not found to have a descriptive MeSH terms. When I typed the term "pump" in the MeSH database, 142 related MeSH terms were found. The majority of the identified search terms were used to describe efflux pumps at the cellular level. In the literature, intrathecal pain pumps are commonly referred to as "intrathecal drug delivery devices (IDDS)". When this term is searched in the MeSH database, no results are found. If the term "drug delivery systems" is searched in the MeSH database, 3 related MeSH terms are described:

1) Drug Delivery Systems: Systems for the delivery of drugs to target sites of pharmacological actions. Technologies employed include those concerning drug preparation, route of administration, site targeting, metabolism, and toxicity.

2) Infusion Pumps, Implantable: Implanted fluid propulsion systems with self-contained power source for providing long-term controlled-rate delivery of drugs such as chemotherapeutic agents or analgesics. Delivery rate may be externally controlled or osmotically or peristatically controlled with the aid of transcutaneous monitoring.

3) Infusion Pumps: Fluid propulsion systems driven mechanically, electrically, or osmotically that are used to inject (or infuse) over time agents into a patient or experimental animal; used routinely in hospitals to maintain a patent intravenous line, to administer antineoplastic agents and other drugs in thromboembolism, heart disease, diabetes mellitus (INSULIN INFUSION SYSTEMS is also available), and other disorders.

The first two terms were identified to be related to the research question. To find literature describing intrathecal pumps delivering different kind of medications or combination therapy for neuropathic pain, each of these terms was entered into the search bar in the MeSH database followed by the enter key and individually combined with MeSH search term “Neuralgia” using the radio button “AND” as per the searches below:

Search **("Drug Delivery Systems"[Mesh]) AND "Neuralgia"[Mesh]**	84
Search **("Infusion Pumps, Implantable"[Mesh]) AND "Neuralgia"[Mesh]**	15

Most of the articles titles using the MeSH terms identified for intrathecal pumps were completely unrelated to the research question and covered a wide array of diagnoses, treatment types and pathologies. It was felt that the search could be more directed using text words to describe intrathecal pain pumps. In the PubMed Search Builder text box I typed “AND intrathecal[tw] AND pump*[tw] to add to the previous search term.

To increase the specificity of articles describing pain pumps used for neuropathic pain, I reselected the MeSH search term “Neuralgia” and clicked the radio button “Add to search builder.” Then in the PubMed Search Builder text box I typed “AND intrathecal[tw] AND pump*[tw] to add to the previous search term. This resulted in the identification of 24 items as per the search below:

Search **"Neuralgia"[Mesh]AND intrathecal[tw] AND pump*[tw]**	24

There were 19 articles remaining using this search when filtered by English. While unrelated titles of articles remained in this search, it was felt to be more specific to the research question. The search was not filtered by humans, as we expected some of the experiments for this non-standardized treatment to be animal-based.

To answer the second part of the research question: the effect of opioids delivered intrathecally, the term “opioid” was typed into the MeSH database and 34 MeSH terms were identified. The first MeSH search term was identified to describe opioids: “Analgesics, opioid”. The search terms intrathecal and pump* were added to the search to specify the route by which the opioids are delivered.

The search started by entering “analgesics, opioid” into the search bar in the MeSH database followed by the enter key. I selected the radio button “Add to search builder”. Then in the PubMed Search Builder text box I typed “AND intrathecal[tw] AND pump*[tw] to add to the previous search term. Then I selected the Search PubMed radio button. These steps built the search strategy that relates to the delivery of opioid analgesics by the intrathecal route and returned 219 items, 197 when filtered by the English language.

Search **"Analgesics, Opioid"[Mesh]AND intrathecal[tw] AND pump*[tw]**	219

The next step was to combine the two components of this search strategy to eliminate articles that appeared in both searches. I clicked on the “Advanced” link at the top of the page that displayed the search results. I selected the hyperlink Add located next to the two queries described above. I chose the “OR” Boolean operator and clicked on the Search radio button. To refine the search, I used the English filter located on the right side of the page. The filters can be selected by selecting “Manage filters” located on the right side of the page. My final PubMed search with the English language filters produced:

Search **((((("Neuralgia"[Mesh] AND intrathecal[tw] AND pump*[tw])) OR ("Analgesics, Opioid"[Mesh] AND intrathecal[tw] AND pump*[tw])) AND English[lang])**	211

I then reviewed the titles for the 211 article reference retrieved from the initial search strategy and identified items to be included or excluded for further investigation. The goal of the initial inspection was to identify articles that provided information on the use of intrathecal pumps for neuropathic pain: safety, adverse events, efficacy and effectiveness.

Inclusion criteria of article references related to three main concepts: treatment, medications, and type of pain. Included treatment types were: intrathecal catheters and pumps. Included medications were those similar to the ones delivered in our research study: opioid analgesics (including morphine, hydromorphone and sufentanyl), local anesthetics, lidocaine, clonidine, and baclofen. Types of pain included were neuropathic pain conditions that would be treated with pain pumps in our study: general neuropathic pain, herpetic neuralgia, neuropathic cancer pain. Articles were included in the initial inspection if the treatment route, medication or pain type was possibly one of the ones listed above.

Exclusion criteria of article references related to three main concepts: treatment, medications, and type of pain. Excluded treatment types were: neurosurgical treatment, combination treatment with spinal cord stimulation, and nerve blocks. Excluded medications were those that would not be administered in our research study: ziconotide, nocistatin, resveratrol, mibefradil, ethosuximide and nickel. Other experimental substances or compounds are not standardly used at intrathecal treatment were also excluded: bovine chromaffin cells, excitatory amino acid receptor antagonists, etc. Types of pain excluded were neuropathic pain conditions that would be not be treated with pain pumps in our study: general chronic pain, headaches, restless legs syndrome, and postoperative pain following cesarean section, gynecologic surgery and cardiac surgery. Miscellaneous exclusion criteria were: comparisons of intrathecal medication delivery to spinal cord stimulation, drug-enhanced spinal stimulation, medical

cost or cost utilization analyses of intrathecal therapies, pediatric catheters, and catheter adaptors.

Evaluation of retrieved articles reference titles identified 107 as possibly relevant to the search topic. Investigation of the abstracts to ascertain further relevance employed the following inclusion and exclusion criteria. Inclusion criteria were: neuropathic pain treated with intrathecal drug delivery on one of the commonly used medications in our research study. Exclusion criteria were: non-neuropathic pain or diagnosis not relevant to our study, alternative route of administration or irrelevant medication used.

Summary

Overall, the final search provided ample material for constructing an evidence-based position on the use of intrathecal pumps. The search strategy yielded a surprisingly large amount of literature pertaining to the safety and efficacy of intrathecal pumps for the treatment of neuropathic pain. Many of the articles reviewed did not address neuropathic pain specifically. However, there is abundant evidence on the use of intrathecal pumps for the treatment of cancer pain, and neuropathic pain often is diagnosed simultaneously with cancer pain.

The search results can be divided into literature that addresses the primary and secondary aims our research project. First we are interested in the efficacy of intrathecal pumps and secondly, the safety and adverse events associated with intrathecal pumps. I chose not to divide the limit the search by one aim or the other; as many of the articles combine these two topics, or provide a general, practice-based opinion on the use of intrathecal pumps. I chose to not filter the search by Humans because I did not want to miss studies performed on animals. As explained in the introduction, intrathecal pumps are a relatively nonstandard practice for patients with neuropathic pain, and animal models provide much of the evidence for them. As a result of the broader scope of the search, more time was spent reviewing reference titles and abstracts to identify pertinent articles. I registered on My NCBI at PubMed, and edited my saved search setting to received future email messages from NCBI on what's new for my saved search.

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