The Bifrost

Preliminary Report

Aadit Shah and Joe Beggs (Group 31)
Client: Dr. Matthew MacEwan

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Background of Problem

A history of misinformation regarding the addictive nature of opioids by pharmaceutical companies and affiliated academic centers led to large increases in such narcotic prescription in the 1990s.[2] Since then, opioid overdose deaths have increased five-fold with the trend predicted to continue.[12] In fact, the number of Americans that succumb to opioid overdose increased by 30% from July 2016 to September 2017.[14] Up to 12% of Americans who are prescribed opioids develop an opioid use disorder. However, the ability of opioids to very effectively treat pain in both acute and chronic settings has led to their continued prevalence. Together, the addictive nature of opioids and their ability to block sensation has lead to misuse deaths accounting for more than 10% of all accidental deaths in the US.[12]

Opioid abuse is especially prevalent in the postoperative patient population. Annually, 14.7% of the more than 51 million Americans who undergo surgery become addicted to opioids, and opioid misuse results in an expedienture of $78.5B for the US alone.[9] In fact, all four guidelines for postoperative pain management indicated by the American Pain Society elect use of analgesics.[5] Even more concerning is that pain management is such a necessity post-operatively that patients who are opioid-tolerant (i.e. history of opioid misuse or overdose) are also onboarded to a pharmaceutical treatment course.

As such, it is pertinent to consider non-opioid mitigators of postoperative pain. Although, this alternative must not forego the beneficial pain blocking effect of the pharmaceutical. These alternatives must provide similar levels of pain inhibition to the current standard of care, not cause addiction, be quantitatively measured/controlled, and be safe for patient use outside of clinic.

Need Statement

A non-opioid method for pain management after surgery that does not require additional surgeries would lead to a better quality of life for patients by eliminating side effects of medication and better control of the pain.

Project Scope

Over 80% of postoperative pain management, even for low-risk surgery, is driven by opioid prescriptions. While these pharmaceuticals are incredibly powerful at abating pain, their highly addictive nature has lead to a misuse epidemic. The team will work to develop a portable solution that blocks pain signals in a non-addictive manner. The treatment course needs to allow patients to autonomously administer pain relief via a safe process that can be quantitatively measured for physician-use. Further, it must not require additional surgeries, cause increased risk of infection/other surgical complications, and be durable enough to function for 4 weeks of postoperative pain treatment. Ideal project completion would be evidenced by such a pain inhibitor that successfully functions in an *in vivo* rat model by December 6th, 2019.

Quantitative Design Requirements

Based on the use case of the patient and the physiology of the nerve meant to be inhibited, our design will have two broad categories of specifications: its ability to safely confer pain relief and its fidelity as a standalone technology (Table 1).

Table 1: A table with key specifications that the solution to manage postoperative pain must conform to.
[1]Considerations for potential solutions that may involve circuitry components.
[2]Not fully waterproof, but resistant to low amounts of sweat and other liquids it may be transiently exposed to. Initial prototype may not be fall proof but the final iteration will require a capacity to survive a minimum of 2 drops from 2 meters.

Specification	Quantitative Metric
Operatable relative humidity range	0-70%
Usable for people in the following age range	12-80
Maximum time to achieve pain blocking effect	5 minutes
Battery life[1]	>1 week
Maximum recharge duration[1]	3 hours
Minimum device durability	28 days[2]
Maximum device dimensions	15.2 cm X 15.2 cm X 7.6 cm (6 in X 6 in X 3 in)
Maximum device weight	1.36 kg (3 lbs)
Maximum temperature of internal circuitry[1]	37.8 °C (100 °F)
Range of atmospheric temperature device can withstand	12.8-37.8 °C (55-100 °F)
Time to completion	5 months
Maximum cost for prototype	$500

In addition to the aforementioned quantitative design requirements (Table 1), it is important to mention other key considerations with regard to accessibility. The device should be usable by the average person. While the device should not require supplementary devices such as smartphones in order to function, bluetooth-based smart-phone integration to track usage or direct WiFi connectivity could be a potential asset for physicians to more accurately manage postoperative patient care. Minimum interaction features of the device include a display with stimulation and power information, and buttons to turn the device on and off and alter stimulation intensity.

The device should not cause any allergic reactions (i.e. use of hypoallergenic materials) and not cause harmful side effects that worsen the patient’s pre-existing condition.

Existing Solutions and Market Landscape

Clearly, the use of opioids must be substituted with an equally effective pain treatment strategy without potential for psychological or physical dependence. Yet other existing solutions remain widely unintegrated into clinical practice. Current non-opioid strategies for pain management will be explored.

Pharmaceutical Approaches

A seemingly obvious alternative is the use of non-addictive pharmaceuticals with reduced potency. The most common pain-killers in the world are nonsteroidal anti-inflammatory drugs (NSAIDs) with more than 30 million users annually (i.e. aspirin, ibuprofen, ketoprofen, and naproxen). NSAIDs do not lead to addiction or dependence and are administered at the site of the trauma/surgery (Figure 1). NSAIDs alone, however, do not relieve moderate to severe pain following surgery.[11] Therefore, NSAIDs are often used in conjunction with patient controlled analgesia (including morphine) following major surgery to reduce consumption and associated side effects. However, these non-opioid pain-killers have side-effects of their own. NSAIDs are associated with prolonged bleeding time and adverse gastrointestinal effects amongst other outcomes.[13]

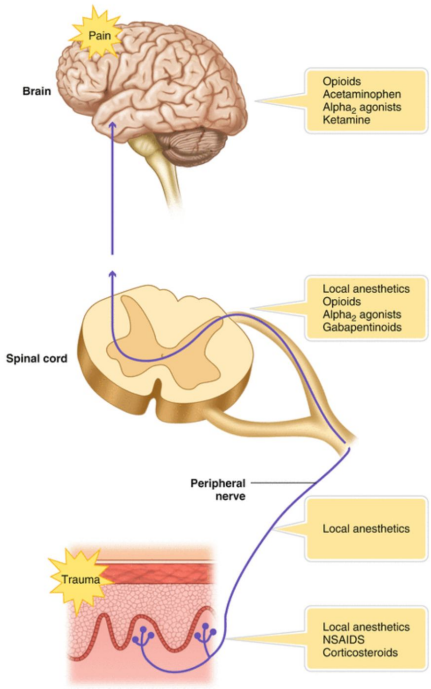

Figure 1: A description of and point of delivery for the various pharmaceutical strategies for postoperative chronic pain management.[6]

Other non-opiate analgesics can be categorized as epidural and spinal analgesia which are used most often for lower abdominal surgeries (as seen in Figure 1). Epidural analgesia, regardless of analgesic agent, location of catheter placement, and type and time of pain assessment, provides better postoperative analgesia compared with parenteral opioids.[2] However, epidural and spinal analgesia is administered into the spinal column of the patient and is likely infeasible for self-administration by the patient in an outpatient setting post-operatively.

Bioelectric Approaches

In recent years, bioelectric pain blocking has been hypothesized as a new mode of analgesia. In the field of bioelectric stimulation, there currently exist three paradigms: direct-to-skin transcutaneous electric stimulation via radio-frequency (RF), nonresorbable battery-powered stimulators that are implanted and subsequently explanted post treatment

course, and immobile (classic) electronic stimulation equipment (e.g. tabletop function generator) to deliver energy via wireless or wired power transfer for implanted nerve blockers.[1]

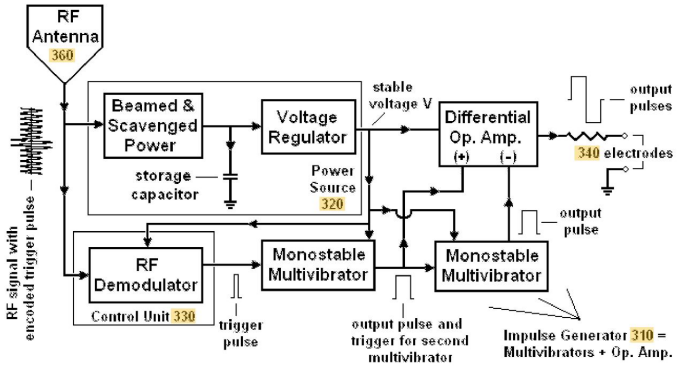

Figure 2: A schematic of a transcutaneous, non-invasive bioelectric vagus nerve stimulator.[18] Note, numbers represent parts referenced in patent application irrelevant to this discussion,

Direct transcutaneous stimulation has been proven to successfully modulate nerve activity. Namely, it has significantly reduced the occurrence of chronic headaches.[10] This technology leverages safe pulses using an RF antenna (Figure 2). However, its use-cases are limited to nerves that lie close to the skin.[18] This is an important consideration as the nerve of interest can be located up to 4 centimeters from the skin in a post-operative pain management

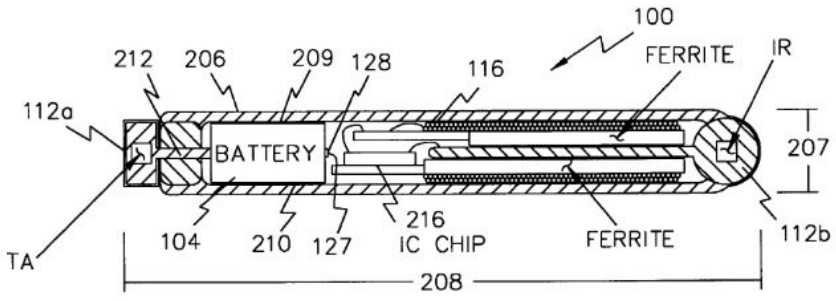

Figure 3: A depiction of a battery-powered implantable nerve stimulator for pain abatement.[17] Note, numbers represent parts referenced in patent application irrelevant to this discussion,

Battery-powered devices house power within the implant itself. This paradigm enables the stimulator to block pain at the site of trauma regardless of the depth from the derma. In fact,

such devices have been developed to fulfill not only pain management but assist organ function.[17] At the same time, clinical implementation poses a multitude of challenges. As seen in Figure 3, the battery occupies a significant volume that increases the overall size of the implanted device. Every centimeter matters when implanting a device. Thus, the additional bulkiness of the battery may limit it from size-contrainted uses. Further, the necessity to explant the battery powered device adds several risks for the patient, especially those with multiple comorbidities. Given that the most common cause for explantation of spinal cord stimulators is inadequate pain control, the potential need to explant and reimplant another stimulator to manage postoperative pain only heightens the surgical risks associated with this treatment course.[7] In addition to explanation for inefficacy of the implant, the battery source may need to be replaced which, again, requires multiple surgeries after the initial operation. However, this problem may be overcome by the relatively recent use of rechargeable power solutions in neuromodulation that have predicted battery lives between 9 and 25 years.[8]

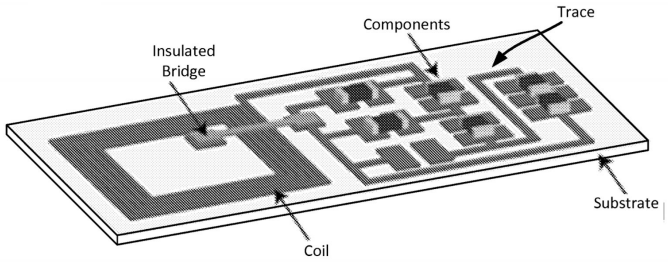

Figure 4: A depiction of a bioresorbable, implantable nerve stimulator.[4]

Other implanted stimulators with external power sources pose risks as well. An excellent example is an implantable, bioresorbable sensor (Figure 4). This technology leverages materials that can be resorbed naturally by host factors over a period of months.[4] These bioresorbable blockers circumvent the need for explantation and remove risks associated with battery-powered and traditional (i.e. non-resorbable) implants. However, even in such a paradigm, the technology is limited by its powering methods. In the wired power modality,

neuromodulation is achieved but the presence of a direct connection from the nerve through the tissue and derma to the environment poses an infection risk.[8] In addition, such wired solutions can reduce patient comfort and mobility.[8] In the case of wireless power transfer, the health risks are diminished, but there currently exists no mobile platform for patient use outside of the clinic. Further, current wireless power transfer relies on RF frequency transmission by bulky electronic equipment that patients can only access in healthcare settings.[4,8] Additionally, RF power transfer efficiency is highly reliant upon alignment of the primary and secondary coils.[20] Ambulatory motion by the patient may disrupt this alignment and cause lapses in power transfer efficiency.

Eastern approaches

Alongside both traditional chemical solutions and newer bioelectric solutions, originally developed for Eastern Medicine, acupuncture has long been used for pain management. The practice involves piercing the skin with a series of small needles at locations called acupoints. These benefits are thought to be derived from the proximity of acupoints with nerves through intracellular calcium ions.[19] Acupuncture has been demonstrated to enhance endogenous opiates, such as dynorphin, endorphin, encephalin, and release corticosteroids, relieving pain and enhancing the healing process.[15] Recently, acupuncture has also been shown to relieve pain following ambulatory surgery.[19] However, some skeptics believe that benefits derived from acupuncture are due to the well-documented placebo effect.[16] In general, acupuncture has been restricted in the West to the treatment of chronic pain which does not include use following surgical procedures.

For clarity, this same information is recapitulated in Table 2.

Table 2: A table outlining the key pros and cons of each of the current non-opioid pain management solutions.

Solution	Approach Category	Pros	Cons
NSAID	Pharmaceutical	Non-addictive and can relieve mild pain	Moderate side effects, may be inadequate for post-operative pain
Other non-opioid analgesics	Pharmaceutical	Excellent method for analgesia	Impractical for administration at home by the patient
Direct-to-skin transcutaneous electric stimulation	Bioelectric	No implanted device required and no additional surgeries required	Nerve of interest must be close to the derma for proper pain inhibition
Battery-powered nerve block implants	Bioelectric	Very few side-effects, can deliver power locally to the nerve Non-addictive and applicable to nerves regardless of depth	Requires additional surgery for explantation and bulkiness of the battery requires additional space within the patient
Resorbable implants with wired external power source	Bioelectric	No need for device explantation post-treatment Non-addictive and applicable to nerves regardless of depth	High risk of infection for percutaneous leads and need for explantation of those leads post-treatment Reduced patient mobility
Resorbable implants with wireless external power source	Bioelectric	No need for explantation of the device because body resorbs internal components Non-addictive and applicable to nerves regardless of depth	Misalignment between power source and implant may cause lapses in power transfer efficiency
Acupuncture	Eastern medicine	Non-addictive, applicable to most parts of the body	Controversial literature surrounding efficacy

Gantt Chart and Design Schedule

Table 3: Gantt chart outlining the proposed project timeline. Team member responsibilities are delineated by color. Green represents Aadit's responsibilities, red Joe's, and blue the team's.

	August	September	October	November	December
Identify Project					
Project Scope					
IP Search and Existing Solutions					
Preliminary Report					
Web Page					
Design Alternatives					
Pugh Chart					
Choose Solution					
Design Solution					
Design User Interface					
Budget and Justification					
Progress Report					
Lemelson-MIT Prize					
Write Software					
Build & Test Hardware					
Test Software					
Individual Presentation					
Verifcation and Validation Report					
Secondary Risk Analysis					
Test Prototype					
Final Prototype Demo and Report					

Team Roles and Responsibilities

Table 4: Project responsibilities broken down by team member.

Name	Responsibility
Joe Beggs	Durability testing & hardware components
Aadit Shah	Software & device compatibility with physiology

With respect to meetings, weekly reports, written manuscripts, and presentations both members of the team will work together. While there is value to assigning pointed responsibilities to a single individual, attending meetings alongside working on progress updates together will ensure the group works cohesively throughout the design process.

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