Sackler Journal of Medicine

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MISSION STATEMENT

What's emerging in medicine today? The Sackler Journal of Medicine – a forum where trends in medicine including translational research, the economics and policy of healthcare, and clinical experiences are explored, analyzed and discussed. SJM is a peer-reviewed journal for medical students to discuss and learn about the latest medical breakthroughs and the fundamentals of medicine.

We encourage student and physician collaboration to bring you literature reviews, case reports, original research, reflective pieces, and short commentaries on published papers. Take the opportunity to contribute your work, experiences and voice to the conversation.

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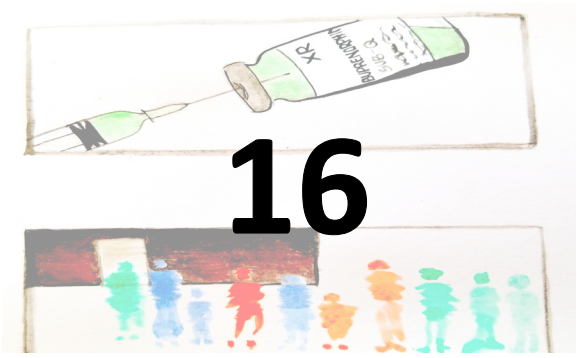
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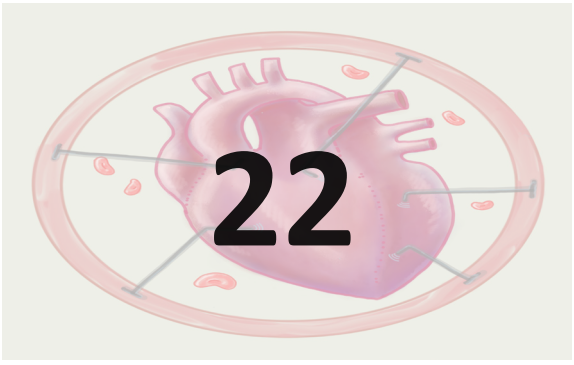
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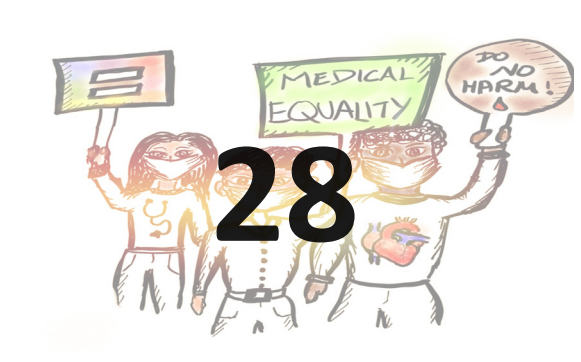
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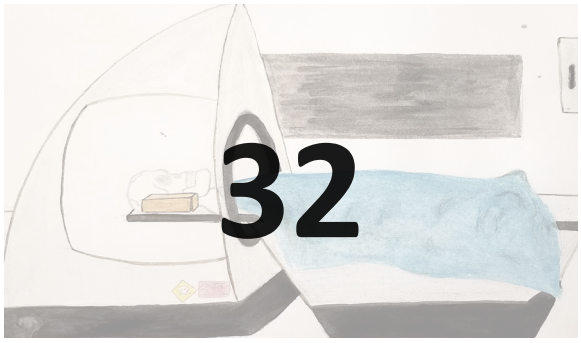
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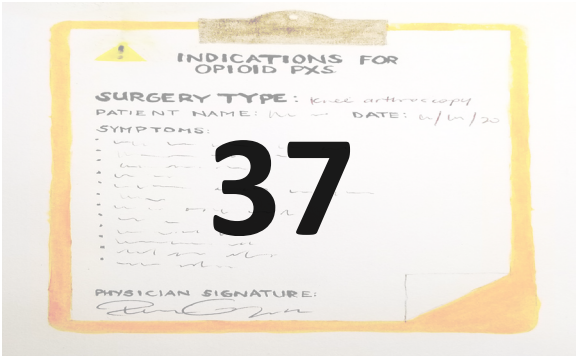
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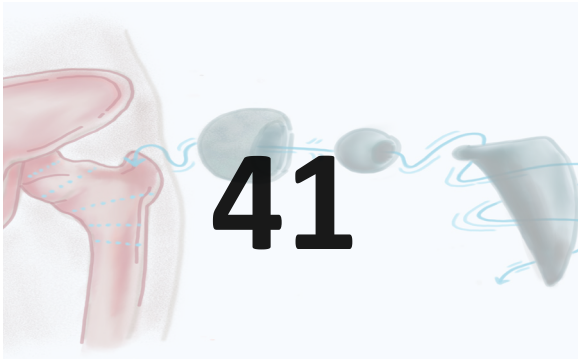
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Letter From the Editors

Dear Sackler community,

If there's any word we could use to describe this year, it would be "contradictions." We've tried to pretend that things are normal and that life goes on, but this year has not been normal, and for many, life has not gone on. Many in the Sackler community and beyond have faced personal and professional challenges they never could have imagined. We have had to deal with illness, death, and economic difficulty in our circles of family and friends, all the while attempting to focus on our studies and our patients. The mental, physical, and emotional difficulties we have faced have led us all to realize, to some degree, that as much as we know about the human body and its manifestations of pain, suffering, and illness, there is still so much more that we have to learn. The trauma and lessons of this year have shaped, and will continue to shape, who we are as people and as future physicians.

Ironically, modern medicine has become very uncomfortable with death. Over the last hundred years, antibiotics, vaccines, drugs, dialysis, ECMO, respirators, transplants, and a host of other discoveries have made death seem like a glitch in the system, a mere technical problem to be overcome, rather than an issue with the system itself. And yet, every now and then something like COVID comes along to remind us that there are still many things beyond our control. The image of the bold surgeon striding into the OR to confidently save another life was replaced by images of overwhelmed, exhausted, and scared doctors and nurses, swaddled in layers of PPE, helplessly watching as yet another ventilated patient succumbed to the virus. Health care providers and civilians alike, for reasons we still do not understand, responded to the virus differently, some presenting asymptomatically, and some declining quickly and dying within a matter of days to weeks. So, while we celebrate the monumental achievements of the medical world this year, we also are forced to accept our limitations.

This year has also driven home just how incredibly important continued involvement in research is. With all that medical students are expected to learn about the things we've already discovered, it can be difficult to remember that it is vital for us to contribute to the continued march of medical progress and discovery. In whatever way we can, an integral part of our medical education is an understanding of the language and techniques of medical research. Most of us have probably had this experience at some point over the past year--friends and family ask us what we think about this study or that, this article about new mutations, and this Twitter thread about the effectiveness of masks. All of a sudden, we were expected to be able to eloquently explain why vaccines and fertility aren't a concern, or to debate the finer points of the latest epidemiological studies. As physicians in the modern era, this ability to distill and clarify information will be one of the responsibilities we must accept. We must be advocates not only for our patients, but for the entire medical and scientific community.

So in that spirit, we bring you this latest edition of the Sackler Journal of Medicine. With this issue, we celebrate new milestones and achievements, while also remembering the many upended and lost lives COVID-19 has left in its wake. It is our great privilege to contribute in some small way to the building of the Sackler research community, and we hope that all of us will achieve ever greater heights in our personal and professional lives.

Thank you to our peer reviewers, manuscript and associate editors, artists, and the Executive Board. We very much couldn't have done it without all of you.

Looking forward to better times ahead,

Shuey Mirkin and Graydon Tope
Editors-in-Chief

Letter From Dr. Allen

Aaron Allen M.D.
Faculty Advisor- SJM
Deputy Director
New York State Program
Sackler Faculty of Medicine
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Israel

"As long as the candle flickers one can still repair"

Dear Sackler Journal of Medicine Readers,

This iconic Hebrew phrase was uttered by Rabbi Israel of Salant upon seeing a shoemaker work late into the night working by candlelight. The meaning however, in folklore has taken a much larger meaning. As long as the light or flame of will is burning all hope is not lost. With the production of this edition of the SJM we feel this acutely. At the moment when medicine has faced one its greatest difficulties in the COVID-19 pandemic we have seen the unprecedented development of the novel vaccine in record time. Here in Israel as we speak the rate of vaccination has outstripped the entire world and the light at the end of the tunnel is clearly in sight.

This is just one example of many in this history of medicine and of the profession of medicine of individuals and teams of physicians and researchers rising up to combat the illnesses and maladies of the world. Together with the heroic activities of health care teams throughout the world once again medicine has distinguished itself as the noblest of professions.

These events should infuse all of us students and physicians alike with renewed drive to pursue excellence in both medical care as well as medical research. The work of the Sackler Journal of Medicine is not only to publish exciting articles which this current issue certainly does but to promote the culture of research as part and parcel of what it means to be a modern physician.

I would like to take this opportunity not only to congratulate the staff of the journal and applaud the contributors but also to try to encourage all of those readers who have not yet started their research careers to get actively involved in the world of medical research. Unlike so many careers, medicine demands renewal and discovery. It is precisely the spirit of crisis that brings the need to innovate and develop. I would encourage all the readers of the journal and its staff to see every patient and indeed every day in medicine as an opportunity to improve and innovate. The drive to help others should be in the clinic but also in the minds and laboratories of medical research and development. Never be satisfied that what is currently being done for your patient is the best that can be done. Seek out new ways to improve the outcome as well as the quality of life of each of your patients.

Each one us can be the future and indeed can not only follow the light at the end of the tunnel but become those you kindle the light and make it brighter!

Wishing continued success and discovery and good health to all.

Relationship between Maximum Voided Volume Obtained by Bladder Diary Compared to Contemporaneous Uroflowmetry in Men and Women

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Abstract

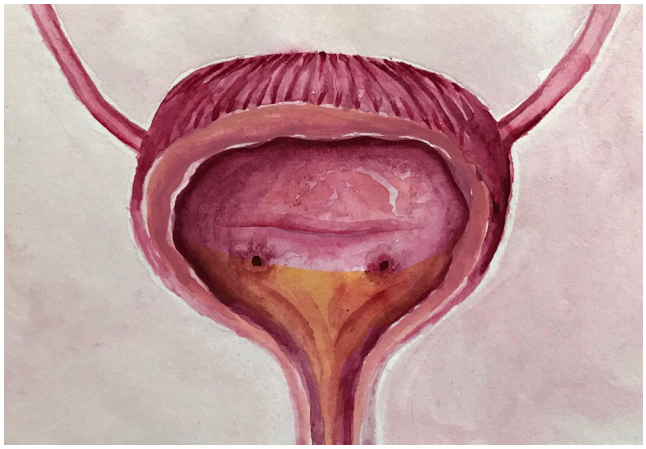
Introduction: Functional bladder capacity (FBC) is an important variable by which lower urinary tract symptoms (LUTS) are assessed. There are two main non-invasive clinical methods by which FBC can be determined - at the time of uroflowmetry (Q-MVV) or during a bladder diary (BD-MVV). By proxy, the maximum voided volume (MVV), obtained by either method, is considered to be the FBC. The purpose of this study is to compare Q-MVV to BD-MVV.

Materials and Methods: This is an IRB approved retrospective study of patients evaluated for LUTS who completed a 24-hour bladder diary and contemporaneous uroflowmetry. For Q-MVV, the patient was instructed to wait to void until s/he felt full. Q-MVV and BD-MVV were extracted from the bladder diary and Q. Pearson's correlation was calculated between the Q-MVV and BD-MVV data.

Results: 771 patients with LUTS completed bladder diaries. Of these, 400 patients (52%), 205 women and 195 men, had contemporaneous Q-MVV. On average, the BD-MVV was 167 mL greater than Q-MVV. In both sexes, there was a weak correlation between Q-MVV and BD-MVV, Pearson's r = .34, ($p<.001$). The difference as a percentage of the larger of the two MVVs was calculated for the 400 patients (D). 172 patients (43%) had a D ≥ 50%.

Conclusions: Functional bladder capacity may be inaccurate by 50% or more when only one of these assessment tools is used. For a more accurate assessment of FBC, both Q-MVV and BD-MVV should be assessed; the larger of the two is a more accurate assessment of FBC.

Abbreviations: Maximum voided volume (MVV), lower urinary tract symptoms (LUTS), uroflowmetry (Q-MVV), 24-hour bladder diary (BD-MVV)



Art by Lital Avni-Singer

Learning points: FBC is an important parameter by which LUTS are assessed with respect to diagnosis, symptom severity, and treatment outcome. Additionally, FBC may be used as a benchmark for behavior modification, or a metric of treatment success. By proxy, both Q-MVV and BD-MVV have been used as a measure of FBC. The purpose of this study is to compare Q-MVV to BD-MVV.

Introduction

Lower urinary tract symptoms (LUTS) are subjective indicators describing lower urinary tract dysfunction that prompt patients to seek treatment. For men and women with LUTS, current guidelines suggest a focused history and physical examination, with simple (optional) adjunctive tests; uroflowmetry (Q-MVV), bladder capacity, post-void residual volume (PVR), and a 24-hour bladder diary (BD-MVV)1,2.

Uroflowmetry measures the flow and force of

urine during a urination. It is commonly performed in an outpatient setting and is a useful and noninvasive test to aid in the diagnosis of urinary tract pathology and to estimate a maximum voided volume. The patient urinates into a funnel which records the force and flow of urine in real time. Urinary symptoms such as intermittent stream, hesitancy, and dribbling can be shown on uroflowmetry. It records any deviation from the norm to assist the physician in making a diagnosis 3.

Bladder diaries are standard tools utilized in clinical assessment of LUTS. Patients with conditions such as benign prostatic hyperplasia, overactive bladder, nocturia, or incontinence may experience a wide range of LUTS and it is important to their clinical manifestations. Multiple factors including bedtime, fluid intake, and urinary output can cause patients to present with different LUTS. The bladder diary offers a snapshot of LUTS in a patient's everyday life and routine. The patient is instructed to record the time and amount of each void for at least twenty-four hours and contemporaneous symptoms with other annotations are recorded for each void. In some cases, oral intake may also be recorded in the bladder diary 4,5.The BD-MVV requires active patient involvement in recording flow volumes and contemporaneous symptoms. When combined with a symptom questionnaire and diligent history taking, it is a very useful adjunct to quantifying LUTS and estimating the functional bladder capacity (FBC), as expressed by the maximum voided volume (MVV). However, patients may find difficulty with adherence and compliance may be low 5. In clinical practice, prior to obtaining Q-MVV, patients are usually instructed to wait until the bladder feels full in order to simulate a natural void. Insofar as most urologists do not utilize bladder diaries, Q-MVV is often the only measure of FBC available to the physician.

FBC is an important parameter by which LUTS are assessed with respect to diagnosis, symptom severity, and treatment outcome. Additionally, FBC may be used as a benchmark for behavior modification, or a metric of treatment success. By proxy, both Q-MVV and BD-MVV have been used as a measure of FBC. The estimated FBC, as expressed via MVV, may be different depending on which of the two methods of estimation were used. The purpose of this study is to compare Q-MVV to BD-MVV.

Methods

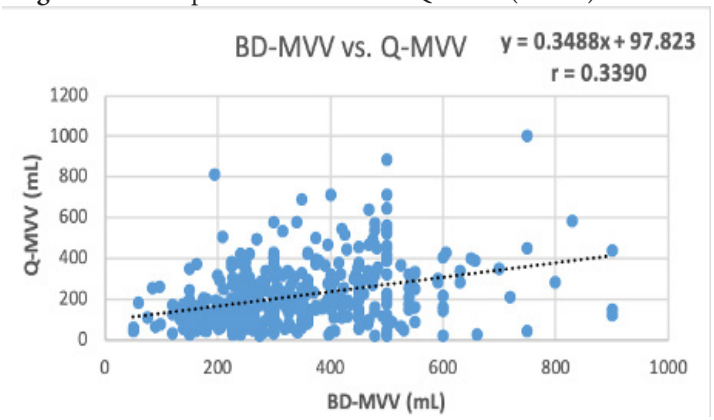
This is an IRB approved retrospective study of men and women evaluated for LUTS who completed a BD-MVV using a smartphone application and a contemporaneous Q-MVV. The following data were extracted from the bladder diary and uroflowmetry for each patient: maximum flow rate (Qmax), Q-MVV, and BD-MVV. Qmax is the maximum flow rate measured by uroflowmetry in the clinical setting. Q-MVV is the maximum voided volume measured by uroflowmetry in the clinical setting. BD-MVV is the volume of the largest void obtained during a 24-hour assessment period recorded independently by the patient in a 24-hour bladder diary.

The data were considered contemporaneous if they were recorded within 3 months of the BD-MVV provided that there were no new treatments or change in symptoms. The contemporaneous Q-MVV was collected in the clinical setting per each patient after they were instructed to wait to void until the bladder felt full. A measure of Qmax and Q-MVV with a full bladder was designed to simulate a natural void to be compared to their BD-MVV. When multiple BD-MVV were completed, the earliest set was used. Additionally, the highest Qmax and lowest PVR were used. Exclusion criteria included bladder diaries without a contemporaneous Q-MVV and those with incomplete or erroneous diary entries. Pearson's correlation was calculated between the Q-MVV measured in the clinical setting and BD-MVV data measured by each patient independently.

Results

771 patients with LUTS, ages 20-94, completed bladder diaries. Of these, 400 patients (52%), 205 women and 195 men, had uroflowmetry data. On average, the BD-MVV was 167 mL (SD 131) greater than the QMVV. A scatter plot depicts the relationship between BD-MVV obtained from bladder diary and Q-MVV obtained from contemporaneous uroflowmetry in figure 1. Analysis of the relationship was performed using a Pearson's correlation. The Pearson's $r = .34$ ($p < .001$), indicating a weak correlation. The BD-MVV was larger than the Q-MVV in 318 patients total. For the female patients the average BD-MVV was 159 mL (SD 133) greater than the Q-MVV (figure 2) and the Pearson's $r = .29$ ($p < .001$). For the male patients the average BD-MVV

Figure 1. Scatterplot of BD-MVV vs. Q-MVV (n=400)



was 175 mL (SD 129) greater than the QMVV (figure 3) and the Pearson's r = .41 ($p < .001$).

The difference between BD-MVV and Q-MVV as a percentage of the larger of the two measurements was calculated for each of the 400 patients (D). 172 patients had a D larger than or equal

Figure 2. Scatterplot of BD-MVV vs. Q-MVV in females (n=205)

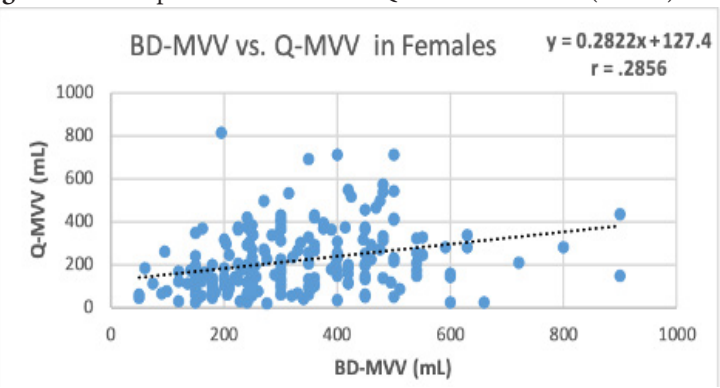
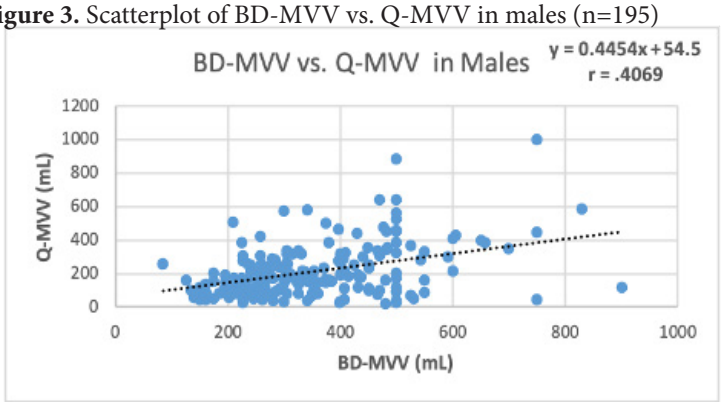


Figure 3. Scatterplot of BD-MVV vs. Q-MVV in males (n=195)



to 50% and 298 patients had a D larger than or equal to 25%.

Discussion

It is intuitive that bladder capacity is an important parameter to include in an assessment of LUTS, but there is no widely accepted consensus on exactly how to measure bladder capacity nor how to define it. Functional bladder capacity, also called MVV, is defined as the highest voided volume recorded on a frequency volume chart 6. Cystometric bladder capacity is the bladder volume at the end of filling cystometry 7. Anesthetic bladder capacity is the maximum amount of bladder distention under general anesthesia and is thought to be a measure of anatomic bladder capacity 8. Another measure of bladder capacity is the largest bladder volume obtained by adding contemporaneous voided volume and post-void residual.

It is well documented that, to a large degree, uroflow is dependent on bladder volume - the larger bladder volume, the greater the flow 9,10. For this reason, patients are usually instructed to wait until the bladder is full before obtaining a uroflow. Hence, in clinical practice, the largest voided volume obtained at the time of uroflowmetry is often used as a proxy for FBC.

While all of these methods of estimating bladder capacity have some clinical relevance, it is intuitive that FBC is the most relevant insofar as it determines the minimum number of times a person must void per day based on the 24-hour voided volume. By definition, the 24-hour voided volume divided by FBC defines the minimum voids required.

There is a paucity of information in the literature about the role that FBC plays in the diagnosis and treatment of patients with LUTS, but there are a number of empiric observations that are clinically relevant. Firstly, in theory, if FBC is increased, for any given condition, the number of voids per 24 hours could be decreased provided that the 24-hour voided volume does not change significantly. Secondly, changes in FBC provide an outcome metric by which the success or failure of treatment is judged. For example, in a phase two study of combination therapy for patients with overactive bladder, the primary efficacy outcome measure was an increase in mean volume voided per micturition 11 . Thirdly, the relation between symptom severity, FBC, and bladder capacity provides a metric for understanding the underlying pathophysiology for developing phenotypes 12. Fourthly, the closer the FBC is to anatomic bladder capacity, the less the reserve for patients to improve bladder capacity by any means other than enterocystoplasty. Finally, FBC provides information that is useful for developing diagnostic and treatment pathways. For example, in a recent

study from our institution, patients with a low FBC (<150 mL), who voided less than 1 L in 24 hours, were older and more likely to have indicators of urethral obstruction or detrusor underactivity than those with an FBC > 150 mL and polyuria 13.

Uroflowmetry has long been considered the first line screening test for most patients with suspected urethral obstruction 14. Since bladder diaries have not gained wide acceptance in urologic practice, the MVV obtained during uroflowmetry is often used as a proxy for FBC.

In contrast to uroflowmetry, the bladder diary is likely to be more representative of the natural home setting; and, as expected, this study confirmed a discrepancy between information obtained through both methods. Advantages of uroflowmetry include a controlled administration environment, less interpretation time, and it is less prone to human error. Disadvantages include cost, and the fact that many patients with LUTS, for matters of expediency, do not wait until the bladder is full before voiding for uroflowmetry. This discrepancy was born out in the current study insofar as the FBC obtained by bladder diary was greater than that obtained at the time of uroflowmetry by an average of 167 mL. For both the bladder diary and uroflowmetry, patient compliance is needed for filling out the diary effectively or arriving to the clinic with a full bladder.

Hofmeester et al. evaluated the agreement between maximum bladder volume (MBV) via uroflowmetry, as measured by adding MVV to PVR, and MVV obtained on a FVC excluding the first morning void. On average, the MVV was 54mL larger than the MBV and the authors suggested that, for most patients, the most accurate assessment of FBC is derived from a frequency volume chart 15.

Ertberg, Møller, & Lose found no differences in maximum bladder capacity (MBC) derived from cystometry, uroflowmetry, and 24-hour bladder diaries in women with urinary incontinence. However, in women with detrusor overactivity, maximum bladder capacity was significantly lower at cystometry compared to bladder diary but noted no difference when compared to uroflowmetry. In women with stable detrusors, no significant difference was observed across any of the three methods of estimation. Women with urinary incontinence and detrusor overactivity are less likely to retain residual urine when measuring MBC via uroflowmetry, therefore their conclusion may be biased. Additionally, the authors compare MBC derived from uroflowmetry and cystometry with FBC derived from 24-hour bladder diaries. FBC must be smaller unless every patient empties their bladder volume completely. We compare two measures of FBC to each other; derived from 24-hour bladder diaries and uroflowmetry voided volume excluding PVR. The authors concluded the low MBC derived from cystometry in women with detrusor instability is likely caused by the cystometric procedure itself because bladder filling can provoke an overactive detrusor contraction 16.

In the present study, on average, the FBC obtained via bladder diary was 167 mL greater than that obtained at the time of uroflowmetry and, whether obtained by Q-MVV or BD-MVV, FBC may be inaccurate by 50% or more when only one of these assessment tools is used. For a more accurate assessment of FBC, the data suggest that both Q-MVV and BD-MVV should be assessed, The larger of the two values defines the FBC.

As is the cas, our study has some limitations. Firstly, although all the patients had documented LUTS, we did not have access to the clinical diagnoses because the de-identified nature of the database did not allow us to see the patients' medical records. Secondly, we recorded the best Q-MVV within 3 months prior to and 3 months post BD-MVV measurement provided that there were no changes in symptoms or treatment, but it is possible that symptom severity and treatment progression could have been skewed because of this relatively long duration between the two measurements. Thirdly, it is possible some patients may not have waited until their bladder was full for the BD-MVV, skewing that data. Fourthly, as this was a retrospective study, many patients had uroflowmetry and bladder diaries at different stages of their treatment and there was no standardization of when these measurements were taken. The inclusion of our patient sample was made on which patients had data, rather than a predetermined group. Finally, we did not consider other measures of bladder capacity such as cystometric capacity or anatomic bladder capacity because those require invasive studies and are not available for most patients.

Conclusions

In this study, the FBC obtained via bladder diary was 167 mL greater than that obtained at the time of uroflowmetry. Furthermore, MVV, whether obtained by Q-MVV or BD-MVV, may be inaccu-

rate by 50% or more when only one of these assessment tools is used. For a more accurate assessment of FBC, the data suggest that both Q-MVV and BD-MVV should be assessed, recognizing that the larger of the two values defines the FBC.

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COMMENTARY/REVIEW

The Importance of Abortion Education in Medical School

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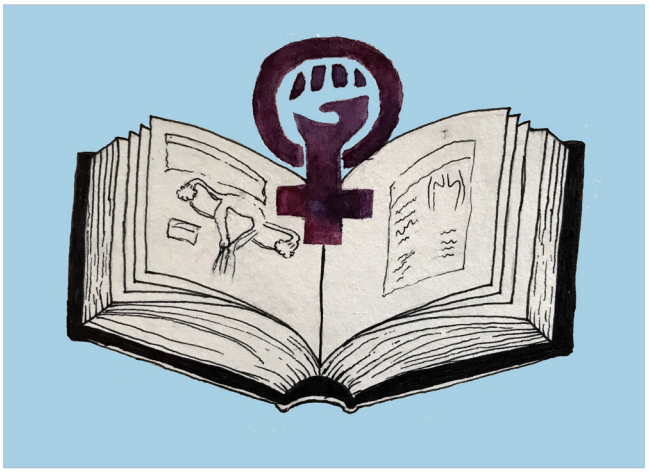

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Since the Supreme Court ruled on Roe v Wade in 1976, abortion is legal throughout the United States. Despite many state laws that attempt to circumvent Roe and limit abortion access by imposing restrictions on when and where a woman can obtain an abortion, women continue to seek and receive abortion care.1 Though not every medical student will become an abortion provider, all graduates will encounter patients who have or who will be affected by abortions.2 In the United States, one in four women will terminate a pregnancy by 45 years of age, while 58% of women of reproductive age live in states that limit abortion rights.3–5

In May 2019, The American College of Obstetrics and Gynecology (ACOG) reaffirmed its belief that abortion is an essential component of healthcare for millions of women. The organization also recommends that all medical students receive opt-out abortion training and education.6 The American Journal of Obstetrics and Gynecology has published several articles reiterating this need, as has the Journal of Obstetrics and Gynecology Canada.7,8 Additionally, the American Medical Association passed a resolution that supports the need for education on safe and effective pregnancy termination and underlines its medical and public health significance.9

Despite these declarations, many medical schools do not include abortion education in their curricula.7,8 This problem may be particularly acute at faith-based medical schools.10 Though research is limited, previous studies have found that the majority of medical students feel it is appropriate to have abortion education in the pre-clinical and clinical curricula, and students who are exposed do find the training valuable.11

The direct impact of the Covid-19 pandemic on access to abortion and reproductive healthcare further demonstrates the relevance and importance of this education.12,13 The ACOG issued a statement in March 2020 defining abortion as an essential procedure that should not be altered by Covid-19 policies.14 However, multiple American states deemed abortion care elective, effectively making abortion unobtainable for patients in those states.13 Across fields of medicine, the pandemic has demonstrated that physicians must participate in public health policy to ensure quality and integrity of patient care during uncertain times. For medical education to be comprehensive, it must prepare students for this role and include abortion procedures.

Abortion is a safe, legal and necessary medical procedure. At a time when access to safe and legal abortion is under threat, it is imperative for all medical students to receive comprehensive, un-biased training in this field.

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ORIGINAL RESEARCH

The First 30 Patients In Israel To Receive Monthly Extended-Release Subcutaneous Buprenorphine

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Abstract

Opioid use disorder (OUD) affects tens of millions of people a year worldwide, with the United States being especially hard hit. Besides for the direct potential of death from overdose, opioid addiction and OUD cause a litany of negative health and societal outcomes. In recent decades, there has been a greatly increased understanding of the role that medication can play in treating individuals with OUD. The two medications most widely used to treat OUD are the opioid agonists methadone and buprenorphine. Buprenorphine has been available for almost 20 years as a transmucosal daily dose, but several extended-release injectable formulations have recently come to market. This report characterizes the first group of patients in Israel to receive this extended-release form, and reviews some of the advantages and disadvantages of these formulations.

Abbreviations: OUD, Opioid use disorder. BUP-XR, Buprenorphine-extended release. MAT, Medication-assisted treatment.

Introduction

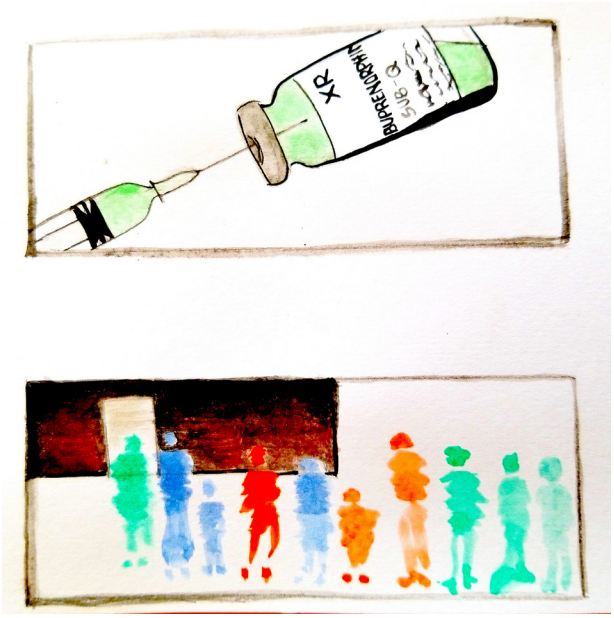
Opioid use disorder is currently defined by the DSM-5 by a series of diagnostic criteria that allow a clinician to classify a patient as having mild, moderate, or severe opioid use disorder. In recent years, the "opioid crisis" has entered common parlance in an unprecedented way. Between the years 1999-2018, nearly 450,000 people in the US alone died because of an opioid overdose, whether prescription or illegal. As of 2019, nearly 5.7 million people in the US were estimated to have used heroin at some point in their lives, and rates of heroin use and opioid use disorder (OUD) doubled from 2002 to 2018.1,2 This crisis has not been confined to the US—rates of opioid prescribing, and of opioid use disorder, have risen dramatically in many countries around the world.1 A 2019 Lancet review estimated that in 2016, there were nearly 27 million people worldwide with OUD, and nearly 90,000 deaths. Death is the most direct negative outcome of opiod use, but there is a vast range of negative consequences from opioid use, including physical and mental health, lost productivity, and the toll on families and communities. There are currently several available medications to treat OUD, the most widely used of which are methadone, a full opioid receptor agonist, and buprenorphine, a partial agonist. Most patients undergoing medication-assisted treatment (MAT) remain on a treatment regimen for many years, if not the rest of their lives, while a minority may eventually be tapered off. Methadone is administered as a daily dose, while buprenorphine is available in several different forms, including a daily transmucosal dose, a 6-month implant, and a monthly extended-release subcutaneous injection. Buprenorphine has several pharmacological and clinical advantages over methadone, including a lower potential for abuse and overdose, but the traditional daily dose transmucosal forms still have the disadvantages associated with any opioid, including overdose, street diversion, and other non-prescribed use.6, 7

Extended-release formulations of buprenorphine seek to address some of these pitfalls, while providing some additional benefits, as well. Freedom from worrying about treatment every day can be psychologically very valuable to patients with OUD, and the extended-release formulations are thought to provide more stable steady-state blood levels, which can help reduce drug cravings and associated withdrawal symptoms.7 XR-BUP has also been successfully used to fully taper patients off of buprenorphine, which for various reasons can be a desirable outcome for many.8 In addition, in light of the COVID-19 pandemic, and the attendant disruptions in medical care that have come with it, it is clear that there is great value in pursuing treatment options

that do not require daily visits to a clinic. These formulations are relatively new to the market, and their effect on patient outcomes is still being determined.7

Between the years 2014-2018, Israel experienced a significant rise in the rate of opioid prescribing relative to other developed countries, according to the Organization for Economic Co-operation and Development (OECD). Israeli data from 2014 to 2018 showed that the amount of defined daily doses (the average maintenance dose per day for a drug, used for its main indication in adults) increased for oxycodone by 27%, tramadol 28%, fentanyl 126%, and transdermal buprenorphine 225%.1, 2, 3

To date, only a handful of studies have been carried out evaluating the effectiveness of extended-release buprenorphine formulations6, 8, 9, and none in Israel. However, reports have been published that survey patients' perception of BUP-XR, and most have found that there is a definite patient preference for BUP-XR. Thus, it is important to carefully follow the experience of these patients to learn more about how the treatment is tolerated long-term. Larance et. al surveyed a group of 402 regular opioid users, and found that 68% thought BUP-XR would be a good treatment option for them, and only 7% expressed a preference for a weekly injection.10 Ling et. al followed a group of 412 patients taking BUP-XR for 49 weeks, and found that patients treated with BUP-XR compared to placebo had stable or improved patient-centered outcomes, as defined by a number of indices.6 Buprenorphine has been available in Israel since 2002 and was added to the list of drugs covered by national health insurance in 2013.2 To expand the available treatment options for OUD, Israel in 2019 became the second country in the world, after the United States, to approve monthly subcutaneous extended-release buprenorphine (BUP-XR). Israel's population of 9 million has about 3,800 methadone and 700 buprenorphine patients in public medication-assisted treatment (MAT) centers, and about 2,000 receiving buprenorphine treatment in private, office-based treatment. Despite COVID-19, during the first two months that BUP-XR was available, 6 public MATs and one therapeutic community center successfully treated 30 patients. All MAT options, regardless of type, cost $55/month at public treatment centers, so there is no financial reason for a patient to prefer one treatment over another.



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Methods

30 patients received subcutaneous BUP-XR between May 1 and July 12, 2020. A 49-item questionnaire was completed via interviews and chart reviews by the medical students and physicians involved in this project, or by the treating physicians and social workers at the treatment centers. This questionnaire assessed patient history with substance abuse, past OUD treatment, reasons for wanting to try BUP-XR, and current living situation.

Patients were administered BUP-XR once a month via a single subcutaneous injection in the abdominal area. Dosages ranged from 8mg to 24mg per injection, with an average of 16mg. 13 patients had previously been on methadone, and 17 patients had previously been at residential treatment centers. All patients administered BUP-XR had previously been treated with standard daily buprenorphine.

Results

Of the 30 patients treated, 77% (23) were male and 23% (7) were female. 40% (12) were immigrants, and 60% (18) were born in Israel. The youngest patient was 24, and the oldest 65, with an average age of 45. 30% (9) were married at the time of treatment, 40% (12) were divorced, 30% (9) were single, and 57% (17) had children. 54% (16) had completed high school, and 13% (4) had pursued higher education. 80% (24) participants were employed. 37% (11) of patients reported a previous criminal record. All of the participants were in treatment for opioid use disorder (OUD), which included 57% (17) using heroin, 10%

(3) using prescription opioids only, and 33% (10) using both.

Methods of opioid intake included 57% (17) via injection, 37% (11) via smoking, 63% (19) via snorting, and 26% (8) oral. Use of prescription opioids included 20% (6) fentanyl, 23% (7) oxycodone, 3% (1) morphine, and 7% (2) unspecified. Sources of prescription opioid obtainment were both by physician prescription and illicit obtainment.

At the time of BUP-XR injection, 13% (4) participants were using illicit substances: 3% (1) opioid, 7% (2) cocaine, and 3% (1) cannabis. 50% (15) of participants had a history of alcohol use disorder, and 3 were regularly consuming alcohol at the time of treatment.

In response to the questionnaire item asking about reasons for wanting to try BUP-XR, almost all patients conveyed that they greatly preferred the convenience and freedom that the once-monthly injection offered them. In addition, 2 patients reported that it was psychologically very valuable for them to not feel like they were dependent on a drug for their daily functioning. 2 patients reported wanting to use BUP-XR as a bridge to total abstinence.

Discussion

Opioid use disorder is a complex and multifaceted phenomenon that has taken many lives and caused a great deal of harm and suffering, especially in the last decade. The importance of medication in the treatment of OUD is only now being fully appreciated, and BUP-XR offers another valuable medication option for treating OUD. As discussed earlier, there are many benefits to BUP-XR, and most patients in this initial study preferred it over the traditional daily form. As BUP-XR is a new treatment option, it is important to carefully track patient experiences in both the short and long-term.

In light of COVID-19, BUP-XR was an especially favorable treatment option for stable patients to reduce the risk of virus transmission.
Patients reported that BUP-XR allowed them to "have a normal life" with less stigma because it freed them from taking daily medication and coming to the clinic regularly.

An interesting phenomenon that some patients reported was that feeling "blocked" for an entire month served as a greater deterrent than daily medication, which could be stopped at any time. Once the injection had been administered, the sense was that they didn't have to devote any more mental energy to it for the rest of the month. This phenomenon is definitely worth exploring, as it may provide a clear advantage over other forms of buprenorphine.

A 1-year follow-up will be conducted to assess if patients saved time and travel expenses, felt less stigma, and overall furthered their lives in recovery; as well as to better identify patient and provider barriers to usage of BUP-XR.

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COMMENTARY/REVIEW

How Telemedicine is Changing Medical Education: Lessons from the COVID-19 Pandemic

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During my third-year clerkships in Internal Medicine and Psychiatry at Tel-HaShomer Medical Center, I allocated a considerable portion of my time in the out-patient clinics, shadowing physicians and treating patients in-house, so to speak. Considering that these clerkships were taking place during the COVID-19 pandemic, many of my patient visits had transitioned from in-person interactions to telemedicine.

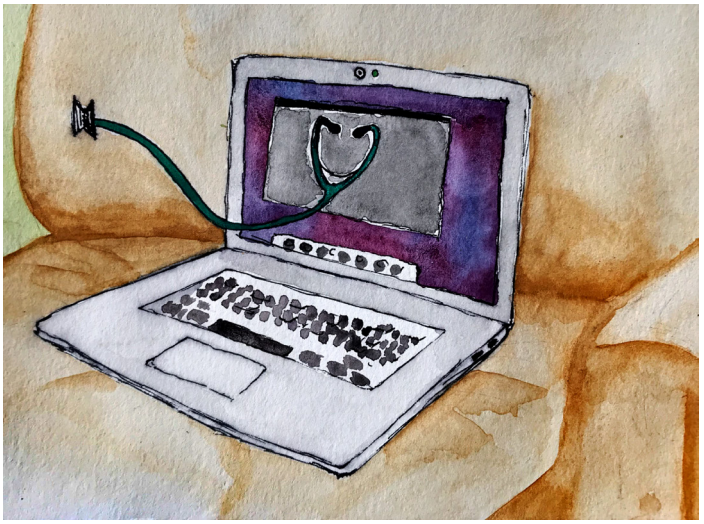
Even with the unpredictable nature of the COVID-19 pandemic, telemedicine has allowed for continuous medical care in many sub-specialties of medicine. Despite both the COVID-19 restrictions and patients' reluctance to travel to the hospital at the risk of exposing themselves to the novel virus, many patients were able to stay on track with their health by maintaining contact with their physicians via telemedicine. Furthermore, having this technology available at our fingertips provides a unique opportunity to see patients that may normally have been lost to follow-up or who may not have originally sought out medical care.

On the other hand, not all visits may be suited for a virtual visit. For example, in cases where the clinical diagnosis is largely based on the physical exam, by examining peripheral pulses or palpating the liver for hepatomegaly, the physician's medical evaluation may be limited, ultimately hindering the timeliness of patient care and treatment. Perhaps even more challenging is creating a strong patient-doctor connection that is felt through a screen. For patients that already have a relationship with the telemedicine physician, establishing this personal connection may not be an issue. However, for a first-time visit, patients may not feel comfortable opening up to someone they have never met before and prefer to meet with someone who they already know.

In addition, some medical specialties may be better suited for telemedicine than others. For example, in psychiatry, the physician does not rely on the physical exam in order to diagnose and treat the patient. Furthermore, psychiatry patients suffering from depression, or other mental illnesses that make it difficult for a patient to readily leave his or her house, may be unable or unwilling to visit the doctor if that requires an in-person meeting. Thus, telemedicine not only allows for psychiatrists to monitor their patients, but also allows for patients to continue receiving the treatment they need.

Albeit different, telemedicine is a particularly suitable option for internal medicine patients, especially those with chronic conditions such as diabetes and hypertension. Both diabetes and hypertension, arguably two of the most pervasive chronic medical conditions in developed countries, require ongoing treatment and regular follow-ups for patients to maintain control over their condition1. Even though these conditions can be monitored in the home setting, doing so takes its toll on the patient overtime. Thus, for patients with adequate management of their condition, the option to follow-up with a physician via a video or phone call allows for greater flexibility in the patients' care. By minimizing the burden of the patient's condition, even if it is by saving them a trip to the physician's office, the hope is that patients with chronic medical conditions will maintain greater adherence.

Besides psychiatry and internal medicine, other specialties such as family medicine, radiology,



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and even neurology and dermatology, are strong candidates for telemedicine due to the nature of those fields' typical visits. However, I believe there is a place for telemedicine in every medical specialty, be it for a follow-up, screening, or a consultation. The direction that telemedicine is going seems to correspond with that notion. New web-based applications and platforms that meet HIPAA requirements are being developed for telemedicine, including some that integrate peripheral devices (i.e. stethoscope, pulse oximetry, otoscope, opthalmoscope, dermatoscope, etc.) to augment patient care2. With new digital tools that accompany telemedicine platforms, neurologists, for example, are able to monitor their patients who have epilepsy via epileptic seizure capture systems, pediatric surgeons can monitor their patients' vital signs and incisions in the perioperative period, and orthopedic surgeons can assess angles of flexion and extension in orthopedic consults via a virtual goniometer3,4,5.

In response to social distancing, the COVID-19 pandemic has allowed for a rapid incorporation of telemedicine across medical specialties. With respect to the future of telemedicine, I suspect that this pandemic is merely a jump-start for its widespread utilization. Perhaps in the future, beyond the pandemic, we will continue to see developments of digital tools used in telemedicine, allowing telemedicine to be an essential means of providing medical care across all medical specialties.

In conclusion, the COVID-19 pandemic has put physicians and medical students to the test of whether patient visits can be accomplished as thoroughly in person versus through a screen. Can healthcare workers extract clinically relevant information in the same modus operandi pre-COVID-19 and still reach the correct diagnosis? Unfortunately, the answer is not clear.

As medical students, we are taught how to perform a physical exam and interact with patients in person. However, if telemedicine is something that will persist into our futures as physicians beyond the current pandemic, then it is important for us as medical students to be trained properly to ensure adequate care for our future telemedicine patients. In the meantime, our job as observers can be to identify any system failures that we see exist in the current telemedicine model so as to improve any pitfalls for the future of telemedicine.

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ORIGINAL RESEARCH

Take it or Leave it, Pacemaker Leads Edition

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Abstract

Background: Lead extraction for cardiovascular implantable electronic devices (CIEDs) can be a risky procedure and currently, there is still a lack of conclusive indications for many non-infectious causes of lead extraction.

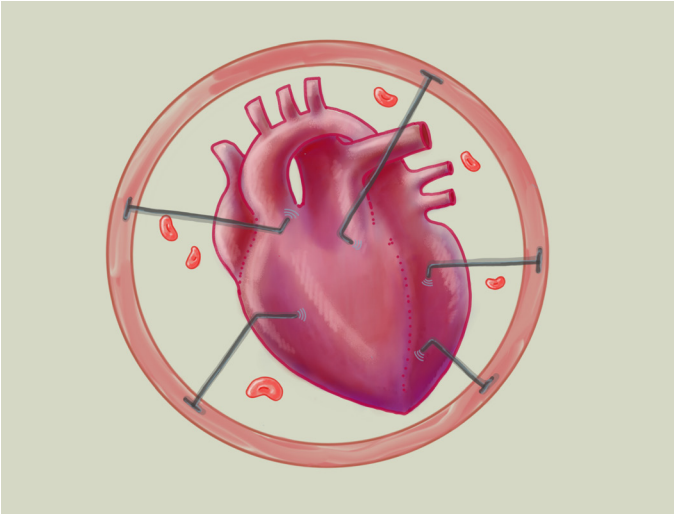
Methods: A retrospective cohort study design was used to look at the indications and outcomes of lead extractions by a single operator at a major referral center in Israel.

Results: A total of 115 lead extractions on 71 patients was performed by a single operator in Tel Aviv, Israel for non-infectious causes between January 2011 to October 2018. The most common complication being bleeding which was significantly related to femoral lead extraction (RR 12.6, CI 10.7 – 14.6). Of the cases that had minor or major complications during lead extraction, 85% of these surgeries were for venous occlusion. Venous occlusion caused 82% of minor complications during surgery (RR 3.95, CI 2.3 – 5.6) and 85% of all complications during surgery (RR 4.09, CI 2.5 - 4.7).

Introduction

Over the past 35 years Cardiovascular implantable electronic device (CIED) use has significantly increased, with now one million new CIEDs have been implanted worldwide annually.1,2 Although these devices have revolutionized the management of patients with irregular heart rhythms, they are associated with various infectious and non-infectious complications which may necessitate their removal.1,2,4 The leads of CIEDs are the device's weakest link,with lead failure rates estimated to occur at a rate of 0.29-0.45% annually.2,4 The most common causes for lead removal include infection, venous occlusion, potential lead malfunction, and mechanical lead failure.1,6,7

Lead extraction is completed in a stepwise manner starting with mechanical tools and progressing to powered-tools such as laser sheaths.8,9 When to switch methods of extraction depends on the type of lead, length of implantation, and operator judgement.4,8,9 Lead extraction is initially approached with mechanical traction and non-powered tools such as a simple lock, followed by femoral extraction and mechanical dilator sheaths such as the Spectranetics tight rail. Subsequently, a laser sheath may be required, particularly in older leads with more tissue fibrosis.8,9



Art by Niko Morozov

Despite advances in lead removal, current estimates from large multi-center reports suggest clinical failure of lead extraction rates ranging from 2.3-3.3%, and major adverse events during lead extraction occur in 1.7-1.8% of patients.8,9 Considering the significant risk for complications, benefits to the patient must outweigh any surgical risks. Little contention exists regarding the necessity of removing infected leads. However, the risk-benefit ratio of non-infected lead removal indications has conflicting evidence for usefulness of lead extraction, as many non-infectious indications for lead removal are currently categorized as class II indications.1 These indications include future threats to patients by lead failure, chronic pain, nonfunctional leads in a young patient, and device upgrades.1,4

This retrospective, single-center study aims to look at the outcomes of lead removal due to non-infectious causes in 71 patients with different CIEDs between 2011-2018, for non-infectious causes. CIED types include pacemakers, pacemakers with implantable cardioverter-defibrillator (pacemaker-ICD), car-

diac resynchronization therapy pacemaker (CRT-P) and cardiac resynchronization therapy defibrillator (CRT-D). The purpose of this study is to provide descriptive statistics related to non-infectious indications for lead extraction and the risk for surgical complications related to these extractions.

Methods

Study Population

This retrospective, single center, cohort study investigated patients who underwent lead extraction for non-infectious causes by a single operator (E.N.) at Sheba Hospital. Sheba Hospital is a tertiary referral centre for cardiac patients located in Tel Aviv, Israel. The cohort had 71 patients who underwent lead extraction for a total of 115 leads, between January 2011 to October 2018. Exclusion criteria were signs of infection, such as fever or positive bacterial culture.

Categories

Non-infectious causes for lead removal included in this study were categorized as broken lead, heart transplant, occluded vein, pain, and lead repositioning. Major and minor adverse events included in this study are in accordance with 2017 Heart Rhythm Society (HRS) guidelines.1 Briefly, major adverse events included any complications that could result in a fatal outcome, while minor complications may require medical management but are neither life-threatening nor require surgical intervention. Complications that were categorized as minor adverse events included bleeding, hematomas, worsened valve function; complications categorized as major adverse events included death, cardiac tamponade, and outcomes that require immediate surgical intervention.

Extraction of the lead was considered a success if the lead was completely removed, a partial success if the residual lead fragment was ≤ 4 cm in the vascular space, and a failed extraction if > 4 cm of the lead remained.12

Statistics

Descriptive statistics for continuous variables including age and years post-surgery were expressed as a mean. Age was expressed with standard deviation of the mean to show the spread of data. Standard error of the mean was expressed in measures of duration since entry to pocket to compare group differences. Discrete variables such as gender, type of pacemaker, and method of lead extraction were expressed as percentages with significance set at a cut off of $p < 0.05$. The relative risk ratio was calculated for factors associated with complications during surgery or lead extraction failures. Confidence intervals were expressed as a 95% confidence interval. Adverse events included any major or minor surgical complications, and extraction difficulties included extraction failure and partial retention unless otherwise indicated. A two-tailed Mann-Whitney test for independent samples was used to find the significance of differences between outcomes related to time passed since the last event.

Results

Between January 2011 to October 2018, 115 endovascular leads were removed from 71 patients. The median age of the cohort was 60 (± 17.1) years old, with 2.8% (n = 2) patients under the age of 18 and 38% (27) patients over the age of 65. The majority of patients were male (77%), 52% of patients were overweight or obese (BMI > 25.0), while 4% of patients were underweight (BMI < 18.5). The most commonly reported comorbidities of the patients were chronic heart failure, hypertension, and diabetes mellitus (Table 1).

The major indications for lead extraction were broken leads at 55% (n = 39), and occluded vein 32% (n = 23) followed by repositioning, heart transplant, and chronic pain (Table 2). Broken leads included leads that had pacing or sensing malfunctions. Venous occlusion included patients who required venous access for a device upgrade but the lead in place caused

Table 1: Demographics of Patients

Age of patient	
Median (years)	60 (± 17.1)
Over 65 (%)	40.3 (n = 27)
Under 18 (%)	3.0
Male (%)	77 (55)
BMI (%)	
Underweight (<18.5 kg/m2)	7.5% (n = 4)
Normal (18.5 - 25 kg/m2)	40.4% (n = 21)
Overweight (>25 kg/m2)	27.0% (n = 14)
Obese (>30 kg/m2)	25% (n = 13)
Comorbidities	
Smoking	14% (n = 10)
Atrial fibrillation	21% (n = 15)
Hypertension	38% (n = 26)
Chronic Heart Failure	49% (n = 33)
Diabetes Mellitus	26% (n = 18)

Table 2: Indication for Lead Removal, CIED Type, Outcome	
Indications for Lead removal	
Broken Lead	55% (n = 39)
Heart Transplant	4.2% (n = 3)
Occluded Vein	32% (n = 23)
Pain	2.8% (n = 2)
Repositioning	5.6% (n = 4)
Type of CIED	
Pacemaker	49% (n = 35)
Pacemaker-ICD	22% (n = 16)
CRT-D	24% (n = 17)
CRT-P	2.8% (n = 2)
ICD	1.4% (n = 1)
Outcomes	
Minor Adverse Events	
Bleeding	14% (n = 10)
Valve Regurgitation	1.4% (n = 1)
Hematoma	1.4% (n = 1)
Total	15.5% (n = 11)
—	
Major Adverse Events	
Sternotomy	1.4% (n = 1)
SVC Syndrome	1.4% (n = 1)
Tamponade	1.4% (n = 1)
Death	1.4% (n = 1)
Total	2.8% (n = 2)
Extraction (115 leads total)	
Partial Failure	1.7% (n = 2)
Failure	6.1% (n = 7)

an obstruction to further interventions. Pain included chronic pain that is intolerable to the patient, and not able to be managed medically.

Of the 115 leads extracted in this study, 1.7% (n = 2) were partially failed extractions with < 4 cm lead retention in the endovascular space, and 6.1% (n = 7) were complete extraction failure with > 4 cm lead retention. Thirteen patients (18.3%) experienced complications during surgery, with major complications occurring in 2.8% (n = 2) patients and minor complications occurring in 15.5% (n = 11) of all patients who underwent lead extraction for non-infectious causes (Table 2).

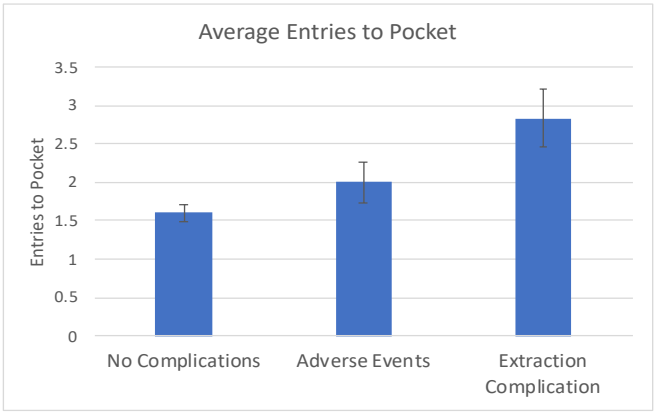


Figure 1: Average entry times to pocket. Mean average was used to calculate central tendency and standard error of the mean was used to express the margin of error. Patients with neither extraction complications or adverse events had 1.60 ± 0.10 entries, while patients with adverse events (both major and minor) had an average of 2 ± 0.27 entries, and patients with extraction complications had an average pocket entry of 2.83 ± 0.37. Adverse events consists of patients who experienced any major or minor complications during surgery, extraction complication represents patients who had partial or failed lead extraction. Details of complications listed in Table 2. Times of entry is not normally distributed. *** A Mann-Whitney test for independent samples determined the difference between extraction complication and the no complications group was statistically significant p = 0.005, while the Mann-Whitney test determined no significant difference between the no complications group and adverse events group p = 0.19.

Figure 1 shows the distribution of the average number of pocket entries. in all patients was higher in patients with any complications compared to all patients, and highest in patients with partial extractions or extraction failures had the highest frequency of pocket entries (Figure 1). Duration since the last intervention or implantation of current device to date of extraction did not vary significantly in patients who experienced surgical complications or extraction difficulties. The average length of duration between extraction and initial CIED implantation in the extraction failure was significantly different from patients who experienced a successful extraction (p < 0.01) (Figure 2A). While the length of time since initial CIED extraction to lead extraction increased risk for surgical complications, the

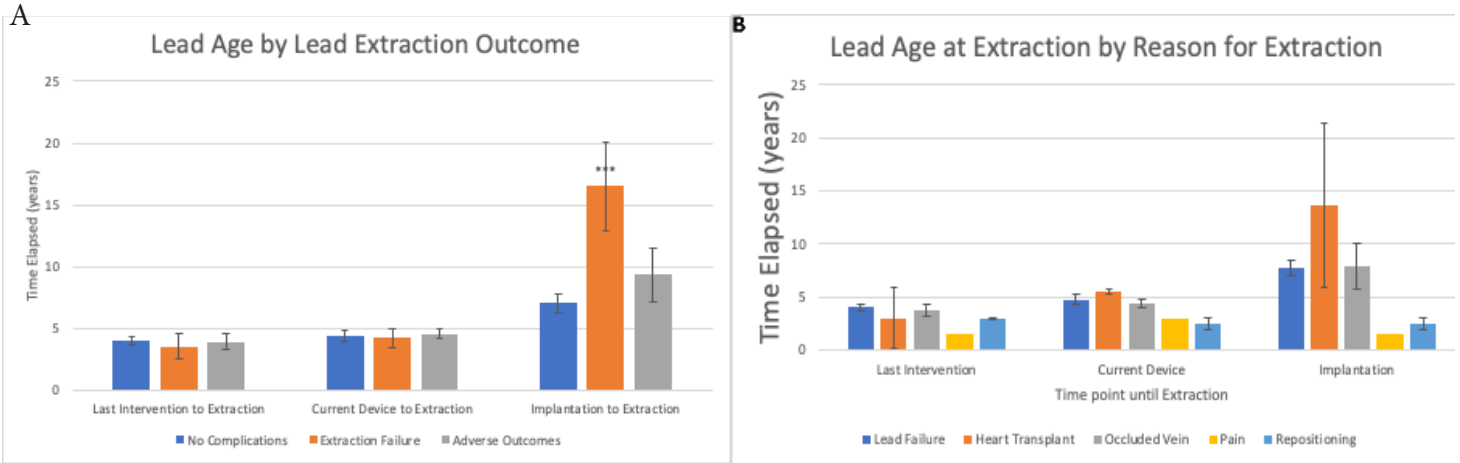


Figure 2. Time elapsed to lead extraction (years). Mean average was used to calculate central tendency and standard error of the mean was used to express error bars. Adverse events consisted of patients who experienced any major or minor complications during surgery, extraction complications represents patients who had partial or failed lead extraction. (A) Time elapsed since initial implantation, implantation of current device, last intervention to pocket in extraction failure and patients with major or minor complications. Mann-Whitney test for independent samples p = 0.28 for no complications versus adverse outcomes group, ***p = 0.001 for no complications versus extraction failure group. (B) Time elapsed since initial implantation, implantation of current device, last intervention to pocket sorted by reason for pacemaker extraction.

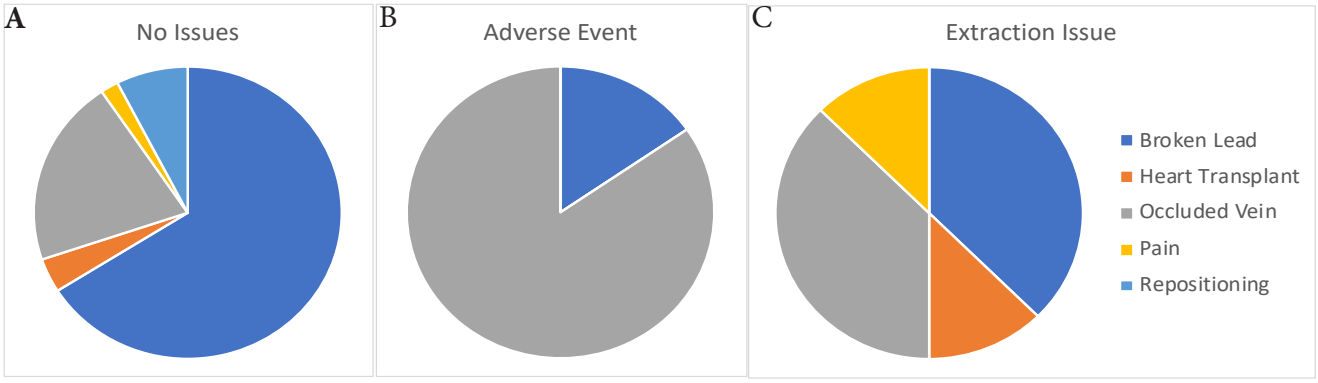


Figure 3. Presenting cause for lead extraction. (A) Reason for extraction in all patients in sample excluding patients with adverse events or extraction issues, (B) Reason for extraction in patients who experienced a major or minor adverse event, (C) Reason for extraction in patients with a partial or failed lead extraction. Chi-squared test ($p < 0.05$) for adverse events sample, showing correlation between reason for extraction and adverse event during extraction. Chi-squared test ($p > 0.05$) for extraction issue (extraction failure or partial extraction) showing weak correlation between reason for extraction and extraction success. Relative risk (RR = 3.95, CI 2.3 – 5.6) for venous occlusion as reason for lead removal in patients with minor surgical complications, (RR = 4.09, CI 2.5 – 5.7) of venous occlusion for major or minor complications during extraction.

risk was not statistically significant ($p > 0.05$). The duration between initial device implantation, current device implantation or last intervention to date of extraction was not significantly different between patients who had lead extraction for a broken lead versus for venous occlusion (Figure 2B).

In all patients, broken lead was the most common cause of lead extraction, followed by occluded vein. However, in patients with major or minor complications, there were more patients who underwent lead extraction for an occluded vein at 85%, the remaining underwent lead extraction for broken lead (Figure 3). This proportion of patients was significantly different than the total patient population ($p < 0.05$). The two patients who experienced major complications from lead extraction were both extractions for venous occlusion, and required laser lead removal (data not shown). The two cases of major complications were SVC syndrome and emergency sternotomy in one case, and tamponade leading to death in the other case. A disproportionately high number of extraction complications were related to patients who underwent extraction for venous obstruction as opposed to broken lead (Figure 3).

For lead extraction, laser was the most commonly used method, being used in 46% of all lead extractions. It was used proportionately less frequently in the group with major or minor complications and extraction failure at 30% and 40% of all leads respectively. However, both cases of major complications from lead extraction were related to use of laser extraction (Figure 4). Femoral lead extraction was associated with significantly (RR 12.67, CI 10.8 – 14.6) more minor adverse events. Specifically of the total 8 leads removed femorally in this study, 6 experienced notable bleeding although no other complications were noted (data not shown). Partial extraction and extraction failures were associated with a higher rate of mechanical and tight rail extraction (Figure 4).

Broken lead was the most common presenting cause for non-infectious lead extraction followed by venous obstruction, however venous obstruction was significantly correlated to more minor and major complications during surgery. Number of entries to the device pocket and duration of time since initial device implantation, last intervention, and since implantation of current device were not significantly different between venous occlusion and broken lead

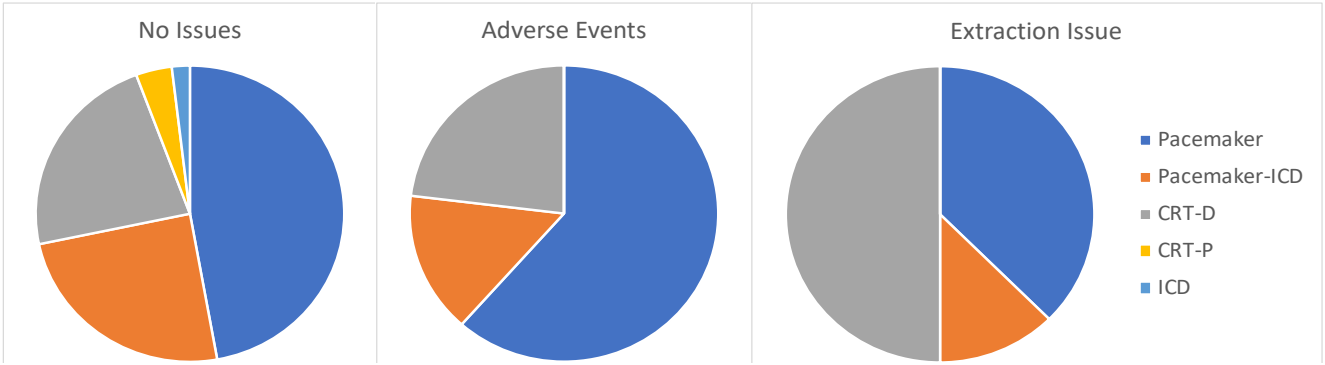


Figure 4. Method of lead extraction by outcome of lead extraction surgery. Leads were extracted in a stepwise manner which was briefly: mechanical, simple lock, femoral, tight rail, and subsequently laser. Extraction failure includes partial (< 4 cm retained lead in endovascular space), and failed lead extraction. Complications include major and minor complications. P value < 0.05 using chi-squared test for method of extraction and risk for extraction failure or complications during extraction. (RR 12.7, CI 10.8 – 15.6) for bleeding by femoral extraction.

groups. Patients who underwent lead extraction for venous occlusion as opposed to broken lead indications were more likely to be a normal weight and under age 65 compared to those with broken leads (data not shown).

Discussion

Our study found that lead extraction for non-infectious causes had a low association for major complications, with only 2.8% of patients having major complications during lead extraction surgery. Duration since last intervention was not significantly correlated with risk of complications during surgery or extraction failures. Increased duration since initial device implantation to extraction showed significant increase in risk for lead extraction failure. Similarly an increased number of accesses to the pocket showed a significant increase in risk for partial extraction or extraction failure.

Femoral lead extraction while often necessary, especially when access to the implanting vein is impossible, is associated with high risk for bleeding and hematomas. Previously, studies have shown that continuation of coagulation therapy does not significantly increase risk of major complications but may increase risk of minor complications such as bleeding.13 As such clinicians who predict a difficult extraction that may require femoral access may exercise caution by investigating coagulation studies prior to surgery.

As CIED design continues to improve, we may see a decrease in the number of non-infectious extraction cases for broken leads and proportionately more cases due to venous occlusion in the future.14 The increased risk for extraction complications or extraction failures in venous occlusions compared to broken leads was not accounted for by duration of current device implantation or duration since last intervention (Figure 2B).

Venous occlusion can occur in chronic indwelling leads although it is often under detected.1 Complete occlusion which would necessitate lead extraction can occur in up to 26% of patients who present with venous occlusion.15 Removal of leads in patients with venous occlusion, particularly when there is a complete occlusion, has the benefits of reducing overall lead burden and preserving the contralateral side for future use.15,16 The risk of extracting leads due to venous occlusion was significantly related to more minor and major complications (RR 4.09, 10.75 – 14.7) in this cohort relative to other indications for lead extraction. The major complication rate of patients in this cohort who had lead removal for venous occlusion was 8.7%, compared to the 2.8% risk of major complications in patients who underwent lead extraction for any reason. The higher risk for complications related to lead extraction may make other methods for lead implantation in patients with venous occlusion such as subclavian venoplasty and tunnelling more appealing. Consideration for which technique to use depends on the volume of lead extractions done at the center and the patient's specific obstruction percentage and lead burden.1,17 As well it is important to consider the patient's age and overall health since presence of abandoned leads may have a higher risk long-term despite the short-term complications associated with lead removal.18

Although current guidelines indicate limited evidence for lead extraction due to chronic pain or heart transplant,1 this study has found no immediate surgical complications or difficulties with extraction in the patients who underwent lead extraction for these indications. Follow-up at later time points with comparisons against matched patients who did not undergo lead extractions may be beneficial to evaluate long term benefits and risks of surgery.

The major limitation related to this study is the limited conclusions that can be drawn from a retrospective cohort study. Since only patients who qualified and underwent lead extraction were tabulated, this specificity leads to a biased sample. Patients were evaluated on a case-by-case basis prior to surgery in accordance to 2009 HRS guidelines and were given alternative treatments if the risk for lead extraction was too high. These protocols automatically select for patients who are good candidates for lead extraction and exclude patients who were high-risk and could have their leads left in place.

Due to the high volume of pacemaker extraction cases referred to Sheba hospital, findings and statistics may vary in hospitals with a smaller volume of lead extraction cases. The relatively low risk of major complications (2.4%) and low rate of extraction failures (7.0%) lends to poor power to predict factors for major complications and extraction failures. Based on these preliminary findings, we hope to contribute to the current body of knowledge on the indications of non-infectious lead extraction indications. Current HRS guidelines classify venous occlusion as a class B indication for lead extraction. Our preliminary findings show a high risk of complications related to lead extraction for venous occlusive causes and cautions further consideration be placed on the

patient's overall health, requirements for future operations and requirement for lead extraction. However due to the small sample size of our single-operator study, further comparison with results from other centers are required for influencing current guidelines.

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COMMENTARY/REVIEW

Racial Biases in Medical Education and the Implications on Patient Care

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Learning Points:

- Current medical education textbooks and resources feature images with a disproportionate amount of light-skinned patients relative to the demographics of the US population.
- A lack of proper education regarding the appearance of pathologies on different skin tones contributes to delayed diagnosis and worse prognosis in minority populations.
- It is essential to (one) recognize the biases that exist in medical education and (two) work to diminish these biases through improved training and resources with images and descriptions across various races and skin tones.

Introduction

Medical students are taught that the first step of any physical exam, before palpation, auscultation, or laboratory tests, is to observe the patient. Visible physical cues can signpost various underlying pathologies. For example, pallor suggests anemia, cyanosis indicates hypoxemia, and certain cutaneous abnormalities may be pathognomonic for infectious diseases. While students do learn a lot by simply looking at a patient, they are primarily taught to do so on one demographic of patients – white patients. Much of the literature provided to educate medical students during their pre-clinical years offers photographs to exemplify skin changes and pathologies, but the patients in these photos are disproportionately white. In reality, the clinical presentations of dermatological findings may be skewed by the patient's skin tone. When the cues students are taught to look for are less apparent on darker skin, the current medical school curriculum focusing on white bodies may contribute to later diagnoses, worse prognoses, and higher mortality in black populations. This paper aims to examine the racial differences in medical training and the consequent clinical implications.

US Demographic Representation in Current Medical School Literature

The United States is referred to as a 'melting pot,' as those residing in the US come from all parts of the world, creating a heterogeneous population of many races and skin tones. In 2019, Americans identifying as non-Hispanic, non-Latinx white comprised 60.1% of the population. The largest minority populations in the United States the same year were Hispanic or Latinx and black or African American, which made up 18.5% and 13.4% of the population, respectively.1 Furthermore, the proportion of the United States population that identifies as non-white is expected to increase, and it is predicted that only 44.3% of the population will identify as white alone by the year 2060.2

However, this diversity is not reflected in the resources used for medical training. When comparing medical course materials to the U.S. population, light skin tone is overrepresented in ¾ of textbooks.3 In order to better understand racial representation in preclinical course material, one study analyzed over 5,000 images from "decks" of slides used in preclinical courses at the University of Washington School of Medicine. When coding for race and ethnicity, 78.4% of these images contained white patients, and 21.6% featured persons of color.4 The discrepancy in representation is even more apparent when looking at skin tone, as opposed to race. This distinction is

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important to note because although some medical textbooks have become increasingly diverse in terms of race, darker skin tones are still severely underrepresented.3 Some of the current top resources for students include Atlas of Human Anatomy, Bates' Guide to Physical Examination & History Taking, Clinically Oriented Anatomy, and Gray's Anatomy for Students. In the analysis of the images from these texts, it was found that the skin tones represented consisted of 74.5% light, 21% medium, and 4.5% dark.3 Medical education goes beyond the organized medical school curricula, as many students, residents, and practicing physicians utilize publications in medical journals to better understand their fields of interest. Unfortunately, analysis of images in medical journals yielded similar findings, with the patients in the photographs being disproportionately white relative to actual patient demographics.5,6

Implications of Racial Underrepresentation

An abundance of studies have long highlighted the disparities in medical care among individuals of different racial groups, subgroups and skin tones.7 Such discrepancies span a multitude of aspects within the medical process, such as time spent with physicians, primary prevention, or even the likelihood of receiving life-saving surgical procedures. The consequences of these apparent disparities ultimately result in a higher mortality and morbidity rate among individuals in minority groups compared to their white counterparts.8 Of the numerous facets that contribute to these statistics, the uneven representation of race and skin color in medical training has been shown to play a role.

This misrepresentation within medical textbooks and training undoubtedly impacts proper medical care of various pathologies, especially on the skin. For instance, physicians miss signs on darker-skinned individuals of diseases that are traditionally visualized on lighter skin. One study found that 47% of dermatologists felt their training did not properly prepare them to diagnose skin diseases in darker toned skin.9 Another study found that medical students were worse at identifying squamous cell carcinoma, atopic dermatitis and urticaria in patients with skin of color. However, they were more accurate at identifying tinea versicolor in patients with skin of color.10 Similarly, questionnaires to general practitioners in the UK found a clear increase in misdiagnosis of melanoma in black patients compared to white patients.11

In melanoma, black and minority ethnic patients have a higher mortality rate despite having a lower incidence. The estimated five-year survival rate for black patients is 70%, compared to 94% for white patients.12 This difference is, in part, because it is initially diagnosed in black patients at a more advanced stage of the disease. Since the prognosis for melanoma is a direct function of disease stage at the time of diagnosis, an early diagnosis can be curable with total excision. However, physicians are trained to identify signs of melanoma on predominantly white patients, even though it can manifest with different appearances and distinct locations on patients with different skin tones. For example, it commonly presents on the trunk in light-skinned individuals but on the foot in dark-skinned individuals. Thus, physicians may not effectively examine the foot, and end up missing live-saving, early detection of melanoma.13 A famous example of misdiagnosis occured in the case of Bob Marley. He had fatal acral melanoma on his toe, which was supposedly initially misdiagnosed as a soccer injury.11 The consequences of uneven representation in medical training likely extends beyond just skin pathologies. Other forms of cancer, such as breast cancer, have decreased survival rates in African Americans compared to white individuals due to advanced initial presentation,13 which could similarly reflect poor knowledge of distinct presentations.

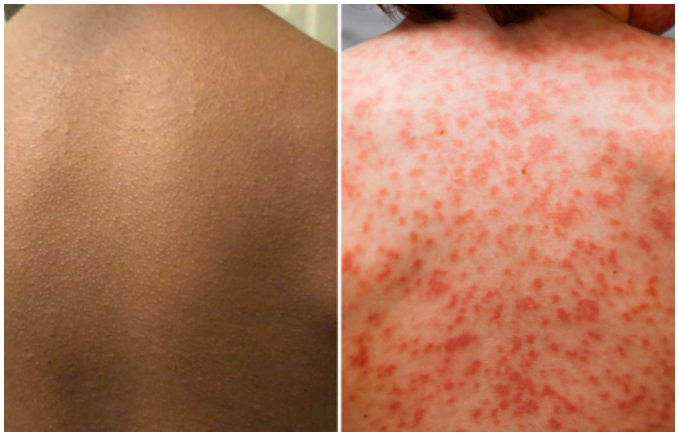

Figure 1. This photo shows an example of Kawasaki Disease presentation on white and dark skin. This photo is from the twitter account, Brown Skin Matters (@BrwnSkinMatters), which posts images of cutaneous findings on different skin tones.

In the case of infections, the tell-tale signs taught to indicate such pathologies are also highlighted in text on light skin, but present differently on dark skin. These different manifestations contribute to later detection and a worse course of disease. Most rashes that are described as erythematous, such as the slapped cheek rash that is pathognomonic for Parvovirus B19 and the maculopapular rash associated with Kawasaki disease [Figure 1], are examples of these manifestations A specific instance of a worse prognosis affiliated with a different rash presentation is in the case of Lyme Disease. Lyme Disease is generally characterized by an erythematous bulls eye

rash called erythema migrans. This red rash is not always apparent on dark skin, so African Americans are less likely to present with erythema migrans. As such, Africans Americans are more likely than white Americans to present instead with late manifestations, such as arthritis, and receive treatment for the infection at a more progressed stage.14

Discussion

As the United States becomes increasingly diverse, medical training emphasizes clinical presentations on white skin. The racially biased portrayal of dermatological findings in medical training has serious clinical implications, such as delayed diagnoses and higher mortality for people with darker skin.

Miseducation in physician training represents a physician-dependent factor. Although many other factors are involved (i.e. genetics, socioeconomics, etc.), it is imperative to examine the role of education on healthcare inequality because we can push for better curriculums and awareness. In order to minimize missed or erroneous diagnoses in clinical practice, changes must occur at the level of medical training. Medical texts should provide images of cutaneous pathologies on a gradient of skin tones in order to better equip physicians to recognize these conditions in the general population, which is far more diverse than is represented in current medical curricula. Some conditions may not be visible upon observation of darker skin – training should account for this and instruct doctors on when to suspect certain pathologies based on other signs and symptoms and to avoid relying solely on pathognomonic rashes for diagnoses.

For instance, one study conducted compared self-efficacy questionnaires to medical students in between an educational module on diagnosing dermatologic pathologies on skin of color. They found that students had greater confidence in diagnosing pathologies on brown and black skin following the module.15 Such findings indicate the benefit in simply having more representation and descriptions within medical textbooks. Many incredible strides to improve education have already been made. One such example is an annotated handbook, called Mind the Gap, made by a medical student in the UK, of clinical signs in black and brown skin.16 Incorporating tools such as this text or the module given in the study could have a significant impact on doctors' ability to recognize pathologies on more diverse populations. Increasing awareness of these misrepresentations as well as implementation of updated training are imperative in providing better healthcare to everyone.

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ORIGINAL RESEARCH

CT Findings in Patients with Early Mortality After Admission to the Emergency Department

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Abstract

Introduction: The purpose of this study was to analyze computed tomography (CT) findings in emergency department (ED) patients with early mortality.

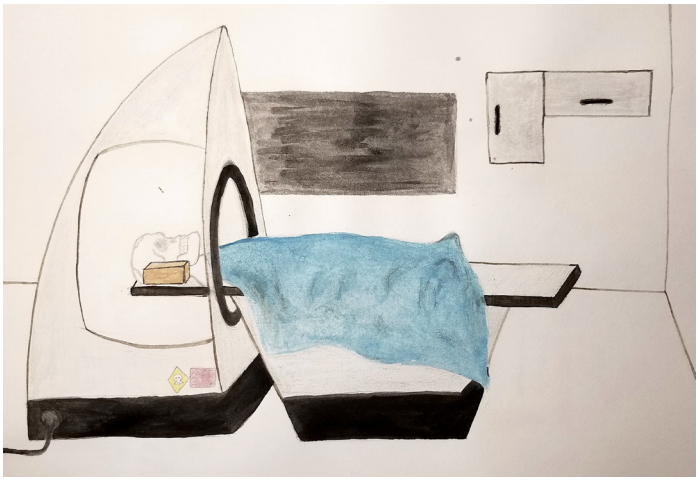
Methods: All patients who underwent CT in our ED from 2012 to 2016 were retrospectively reviewed. Patients with early mortality, which was defined as mortality in the same day or the following day from ED admission, were included. CT interpretations were compared to the cause of death. CT findings which matched the cause of death were included in the analysis. The CT scans were grouped according to organ system (neurological, gastrointestinal, pulmonary, cardiovascular and musculoskeletal). The relevant findings for each organ system were analyzed.

Results: A total of 439 patients underwent CT in the ED. Data were available for 382 patients who comprised the study cohort 382/439 (87%). 242/382 (63.3%) CT findings were associated with the cause of death. The distributions of findings according to the organ system were: neurological 47.5%, gastrointestinal 21.9%, pulmonary 16.5%, cardiovascular 11.2% and musculoskeletal 2.1%. The most common findings were: intracranial hemorrhage (25.6%), traumatic brain injury (12.8%), pulmonary infection (10.3%), rupture of abdominal aortic aneurysm (6.6%), pulmonary embolism (5.0%), mesenteric ischemia (5.0%), bowel obstruction (4.1%), bowel perforation (3.7%), colitis (3.3%) and brain mass (3.3%).

Conclusion: More than 60% of ED patients with early mortality had associated findings on CT . About 50% of the findings are seen in head CT, and intracranial hemorrhage is the commonest overall finding. Knowledge of CT findings associated with early mortality may help in ED patients' management and triage.

Introduction

Computed tomography (CT) imaging is a crucial diagnostic tool used in emergency medicine. This modality is fast and accurate, with high image quality, availability and relative affordability 1,2 . It is the primary and most effective diagnostic tool for multiple conditions such as trauma, pulmonary embolism and acute abdominal emergencies 3,4.



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Understanding of early hospital mortality is important as clinicians strive to make efficient medical decisions about severely ill patients 5.

Previous publications have addressed the issue of early hospital mortality and experimented with predictive models such as nurse assessment, vital sign tests and observations of heart rate signals and pre-hospital end-tidal carbon dioxide in hopes of improving care for patients that are admitted in a critically ill state 5-9. Since CT is one of the main diagnostic tools in the emergency department (ED), understanding CT findings related to early death can help in patients' triage and management.

The purpose of this study was to analyze CT findings in ED patients with early mortality.

Materials and Methods

An institutional review board approval was granted for this retrospective study, and informed consent was waived.

Study Cohort

CT findings of ED patients with early mortal-

ity, which was defined as mortality in the same day or the following day upon admission to the ED, were included in this study 10,11. The CT scanner utilized for the study was a Brilliance 256 (Philips, Eindhoven, the Netherlands).

The hospital's electronic medical records (EMR) were scanned for all adult patients (≥18 years of age) who presented to the ED with early mortality in a time frame of five years, from January 1, 2012 to December 31, 2016. All consecutive patient data demonstrating early in-hospital mortality and with CT imaging upon admission to the ER were included in the final cohort. Patients with missing clinical data or CT interpretations were excluded.

For every patient included in the study, two board certified radiologists (EK with 10 and MY with 5 years of experience) reviewed the CT reports and compared them to patients' cause of death as described in the patients' EMR. CT findings which matched the cause of death were recorded. The CT scans were then grouped according to five organ systems (neurological, gastrointestinal, pulmonary, vascular and musculoskeletal). The relevant CT findings for each organ system were recorded. Findings were also distributed according to two age groups: ages 18 to 50 and over 50 years of age; trauma related mortality increases with age and this stratification may provide meaningful data on early mortality imaging when comparing the two populations.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) and percentages for categorical variables. A two-tailed P value <.05 was considered statistically significant. Data analysis was performed using Python (Version 3.6.5 64 bits).

CT scans for neurological, gastrointestinal, pulmonary, vascular and musculoskeletal association with early mortality and the five findings of each organ group were analyzed. Evaluation of the distribution of CT findings was conducted using chi-square goodness of fit analysis.

Results

Between the years 2012 - 2016, there were 591,887 ED visits, of which 307,974 were adult patients to our general ED. CT scans were performed in 87,428 ED visits (14.8%). Early mortality was present in 2,222/307,974 (0.7%) patients. Of the patients with early mortality, 439/2,222 (19.8%) underwent CT scans. Data was available for 382/439 (87.0%) who comprised the final study cohort included in the analysis. Table 1 presents demographic and clinical data for the study group (n=382). The average age of the included patients was 75.9 ± 15.6 years of age.

CT findings were associated with the cause of death

Table 1: Demographic and clinical data for the study group

Feature:	Values:
Number of patients	382
Age	75.9 ± 15.6
Gender	M:197, F:185
Died in ER : Died in hospitalization department	89 : 293
Five most common past illnesses	HTN: 46.0%, DM: 21.8% Hyperlipidemia: 20.5%, IHD: 18.4%, AF: 11.7%
ESI	2.0 ± 0.8
Vital signs	SBP: 120.2 ± 44.2, DBP: 66.7±24.2, Fever: 36.3±1.5, Saturation: 91.8±10.5

Abbreviations: HTN hypertension; DM diabetes mellitus; IHD ischemic heart disease; AF atrial fibrillation; ESI Emergency Severity Index; SBP systolic blood pressure; DBP diastolic blood pressure

Table 2:

Cause of death in 140 patients in whom ER CT did not show findings associated with the cause of death

Cause of death:	Frequency:
Septic shock	55/142 (38.7%)
Unknown	32/142 (22.5%)
Cardiac ischemia or failure	26/142 (18.3%)
Pneumonia/Respiratory failure	12/142 (8.5%)
Oncology	8/142 (5.6%)
Trauma	6/142 (4.2%)
Ischemic CVA	2/142 (1.4%)
Bowel obstruction	1/142 (0.7%)

Abbreviations: CVA cerebrovascular accident

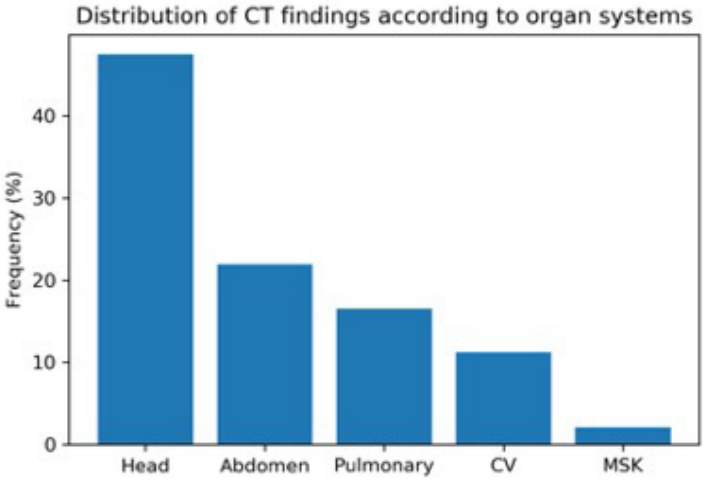

Figure 1: The distribution 242 CT findings according to organ system

in 242/382 (63.4%)of patients. Table 2 presents the cause of death in the 142 patients in whom ED CT did not show findings associated with the cause of death.

In two trauma patients, the cause of death was attributed to both head and body injuries, each counted separately. The distribution of the 242 CT findings according to organ systems were: neurological 47.5% (115/242), gastrointestinal 21.9% (53/242), pulmonary 16.5% (40/242), cardiovascular 11.2% (27/242)and musculoskeletal 2.1% (7/242), and is presented in Figure 1. For each organ system, the CT findings associated with early mortality were separated into the top 5 categories (where available). Table 3 presents the top CT findings associated with each organ system. Non-traumatic intracranial hemorrhage, which is the largest group of findings, consisted mainly of intraparenchymal cerebral hemorrhage 52/62 (83.9%), subarachnoid hemorrhage 4/62 (6.5%), subdural hematomas without known traumatic event 4/62 (6.5%) and bleeding brain masses 2/62 (3.2%).

Table 3: Top five CT findings associated with early mortality in each organ system

Finding	Head (115 total)	Abdomen (53 total)	Pulmonary (41 total)	Cardiovascular (27 total)	Musculoskeletal (7 total)
1	Non traumatic intraparenchymal cerebral hemorrhage 62/115	Mesenteric ischemia 12 / 53	Pulmonary consolidations* 25/41	Rupture of AAA 16/27	Cervical spine fracture 4/7
2	Traumatic brain injury 31/115	Bowel obstruction 10/53	PE 12/41	Signs of cardiac failure or ischemia 6/27	Necrotizing fasciitis 1/7
3	Brain mass** 8/115	Bowel perforation 9/54	Chest trauma 3/41	Thoracic aortic dissection 5/27	Lower limb fracture and hemorrhage 1/7
4	Brain edema due to anoxia 8/115	Colitis 8/53	Lung mass 1/41		
5	Ischemic CVA 6/117	Abdominal mass 5/54			

Abbreviations: CVA cerebrovascular accident; PE pulmonary embolus; AAA abdominal aortic aneurysm
*Pulmonary consolidations in patients with a clinical diagnosis of pneumonia
**Mass effect without bleeding

Table 4: Top five CT findings for two age groups: ages 18 to 50 and over 50

Ages 18 to 50 (32 patients, 25 findings)	Over 50 (350 patients, 217 findings)
TBI (6)	Intracranial hemorrhage (58)
Intracranial hemorrhage (4)	TBI (25)
Brain mass (4)	Pulmonary consolidations (25)
Signs of cardiac failure or cardiac ischemia (4)	AAA rupture (16)
Other findings, one of each	Mesenteric ischemia (12)

Abbreviations: AAA abdominal aortic aneurysm; TBI traumatic brain injury

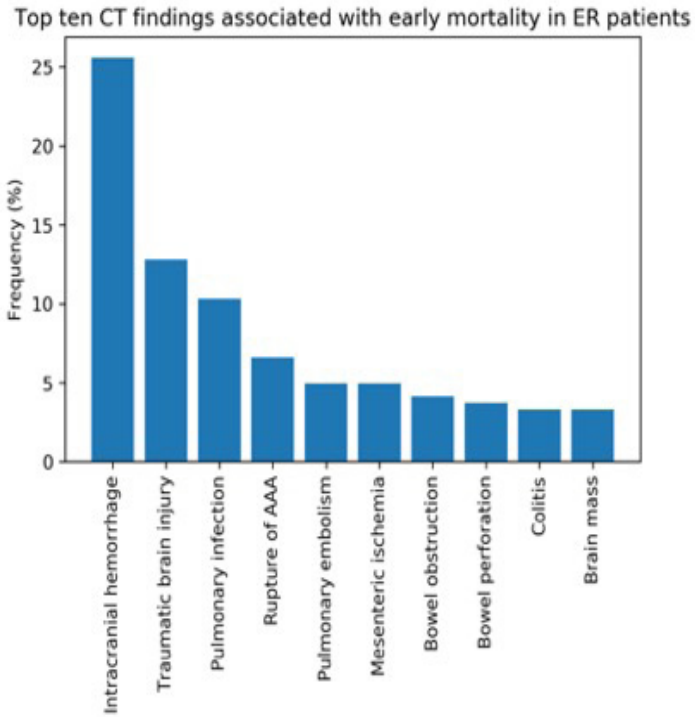

Figure 2: Top ten ER CT findings associated with early mortality

The top five findings in each organ system were compared. Intracranial hemorrhage was found to be the leading CT findings associated with early mortality comprising 62 of the 242 CT findings associated with early mortality ($p<0.001$). The overall top ten findings are presented in Figure 2.

Table 4 presents the top five CT findings for two age groups: ages 18 to 50 and over 50 years. Head CT abnormalities were the most frequent findings both in the younger (56.0%) and in the older (49.8%) group.

Discussion

Understanding of causes of early mortality

in patients admitted to the ED may help in patients' management. The fact that CT scanners are more commonly found within EDs presents an opportunity to perform CT scans early for patients in order to identify any potential associations with possible early mortality. We set out to analyze our ED CT findings as associated with early mortality for multiple conditions.

The study was conducted at one large tertiary care hospital with about 1,100 beds and approximately 185,000 ED visits per year.

Starting with a large group of about 300,000 patients who presented to our ED in a five year period, we found that 0.7% of them had early mortality and about 20% of those underwent CT in the ER. Our results showed that of the 382 ED patients with early mortality and CT scans, more than 60% had imaging findings associated with their cause of early death. Perhaps CT scans were underutilized in the ED of our facility. This poses an area for future research to explore; how does the volume of CT in traumatic cases correlate with mortality prevention?

About half of the findings were seen in head CT scans, and in patients younger than 50 years, head CT findings comprised 60% of the findings. Of the top listed findings, non-traumatic intracranial hemorrhage was the most common, comprising 26% of all findings. The second most common cause of death was traumatic brain injury (13%) and the third was pulmonary consolidations in patients with a clinical diagnosis of pneumonia (10%). The most common causes of death in patients in whom CT findings were not associated with the cause of death were septic shock (39%), unknown (21%) and cardiac ischemia or failure (19%).

As our study analyzed the subgroup of patients who underwent CT in the ED, the distribution of causes of death is different from previous studies 10-14. Jayawardena et al., who analyzed 189 autopsies of patients who died within 48 hours from ED admission, found cardiac related death (27.5%), blunt trauma, mainly head trauma (20.1%), intoxication (13.8%), penetrating trauma (13.2%) and pulmonary thromboembolism (7.9%) to be the most common causes of death 10. Alimohammadi et al. analyzed causes of death in 2907 patients who died within 48 hours from admission to the ED and found cardiovascular diseases (39%), trauma (19%) and cerebrovascular accidents (18%) to be the most common 11.

By understanding the most common CT findings associated with early mortality, patient care may be improved. We recommend that the predictive capability of CT imaging for in-hospital mortality assessment should be further explored.

Our study has limitations. The study was done retrospectively; therefore, we could not control record keeping of the patients used in the study. Additionally, this study was conducted at a single medical center. We chose the grouping of organ systems and findings in a way that, in our opinion, best reflects the clinical significance of the results, but the grouping can also be conducted in other ways. Lastly, the medical causes of death were retrieved from patients' death notes that are based on clinical assessment and our study lacks autopsy results.

Conclusion

Findings are seen in more than 60% of ED patients with early mortality that underwent CT. About 50% of the findings are seen in head CT, and intracranial hemorrhage is the most common overall finding. Knowledge of CT findings associated with early mortality may help in ED patients' management and triage.

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Evaluation of Opiate Use After Knee Arthroscopy

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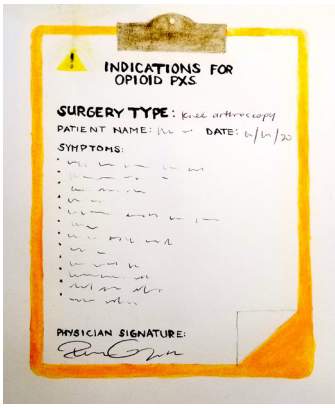
Introduction

Prescription opioid use has increased dramatically in recent years, with the number of prescriptions quadrupling from 1999 to 2015.1 Paralleling this trend has been a nearly identical rise in opioid-related morbidity and mortality.2,3 In 2015, opioids were responsible for over 33,000 drug overdose deaths with half due to prescription opioids.1 The prescription opioid epidemic in the United States has received increased attention in the media due to rise in opioid related morbidity and mortality. As a result, physicians are pressured to be more responsible in prescribing opioid medication, however efforts to do so have been complicated by the emphasis on quality of care metrics such as pain control and patient satisfaction that incentivize physicians to overprescribe.4 Additionally, there is limited information to guide physicians toward safer practice. More than half of non-medical opioid users obtain their drugs from overly prescribed family and friends. It has been suggested that reducing the availability of prescription opioids at the population level could combat this rising trend of narcotic abuse.2

With orthopaedic patients comprising a significant portion of opioid users, it is crucial to have refined practice in prescribing of post-operative opioids in this patient population. The focus of this research was to identify pre-operative factors that may predict opioid consumption.



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Methods

With approval of the institutional review board, we conducted a prospective observational study of 221 patients undergoing various outpatient knee arthroscopy. Procedures eligible for inclusion were meniscal repair, partial meniscectomy, loose body removal, debridement, and chondroplasty. Exclusion criteria were age <12, revision repair, preoperative opioid consumption >1 month, or Workers' Compensation as these patients are known to require higher doses of opioid on average and could skew the results.

Participants filled out a preoperative questionnaire at time of enrollment. Questions regarded smoking status, alcohol consumption, psychiatric medication use, preoperative pain severity and duration, preoperative opioid and non-opioid analgesic use, and the Connor-Davidson Resilience Scale to assess ability to cope with stress.

In this observational study, no changes were made to the surgeons' intraoperative and postoperative procedures and protocols. For example, weight bearing restrictions and analgesic prescriptions were left for the surgeon to decide. Participants were allowed to use any over-the-counter non-opioid analgesics as they found necessary. The surgical procedures were performed at a single orthopaedic-only outpatient center.

After the surgery, participants completed a daily pain diary logging their daily pain level (0 to 100 points) and quantity of opioids, NSAIDs, local anesthetic, and regional anesthetic block used. Data was tracked for the first 7 days postoperative and on the first postoperative visit, usually 10 to 14 days after surgery. Total opioid use was calculated from number of remaining pills at 2-week and 6-week

post-operative visits, then scaled to hydrocodone 5 mg equivalents. Additional variables were assessed for correlation with opioid consumption, including: age, sex, BMI, PROMIS anxiety, depression, pain interference, and physical function.

Results

Table 1 shows the distribution of baseline variables: smoking status, psychiatric medical use, preoperative pain severity and duration, and preoperative opioid consumption for <1 month. Table 2 outlines the distribution of surgical variables such as: surgical procedure, initial opioid prescription, and prescription of nonsteroidal anti-inflammatories (NSAID).

Total opioid consumption ranged from 0-188 pills, with a median of 7 pills (Fig.1 and Table III). 50% of patients took 5 pills or fewer, 80% took 20 pills or fewer. More than 50% of patients stopped using opioids three days after surgery (Fig. 2). The vast majority (88%) of patients had excess opioid medication at the final post-operative follow up. Patients who underwent meniscal repair (odds ratio 7.9, 95% confidence interval 1.8-35.7), smokers (OR 11.9, CI 2.0-71.7), and pre-operative opioid use (OR 7.7, CI 1.2-50.0) were more likely to consume greater than 20 pills (Fig 3). Interpretation of these values is somewhat limited by small sample sizes. There was an association between higher initial opioid prescription and greater consumption. No association was seen between age, sex, weight, BMI, alcohol

TABLE I Preoperative Patient Characteristics

Characteristic	Value
Age* *(yr)*	46.2 (14 to 76)
Sex†	
Male	114 (51.6%)
Female	107 (48.4%)
Weight* *(kg)*	87.8 (49.9 to 181.9)
BMI* *(kg/m²)*	29.0 (17.2 to 70.0)
Smoking status†	
Nonsmokers	212 (95.9%)
Smokers	8 (3.6%)
Not reported	1 (0.5%)
Alcohol use†	
Never	39 (17.6%)
<1 time/mo	44 (19.9%)
<1 time/wk	36 (16.3%)
1 to 3 times/wk	72 (32.6%)
>3 to 6 times/wk	21 (9.5%)
Daily	9 (4.1%)
Psychiatric medication†	
No	173 (78.3%)
Yes	39 (17.6%)
Not reported	9 (4.1%)
VAS knee pain severity* (0 to 100) *(points)*	39.5 (0 to 100)
Knee pain duration†	
1 wk to 1 mo	24 (10.9%)
>1 to 3 mo	59 (26.7%)
>3 to 6 mo	42 (19.0%)
>6 to 24 mo	63 (28.5%)
>24 mo	29 (13.1%)
Not reported	4 (1.8%)
Preoperative opioid usage† (<1 mo)	
No	215 (97.3%)
Yes	6 (2.7%)
Connor-Davidson Resilience Scale score*† *(points)*	33.1 (13 to 40)
PROMIS scores*	
Anxiety	47.4 (32.9 to 71.6)
Depression	43.6 (34.0 to 68.7)
Pain interference	60.1 (38.6 to 75.3)
Physical function	41.1 (20.0 to 73.0)

*The values are given as the mean, with the range in parentheses. †The values are given as the number of patients, with the percentage in parentheses. ‡In this score, 0 is the least resilient and 40 is the most resilient.

TABLE II Distribution of Surgical Variables*

Variable	No. of Patients
Primary surgical procedure	
Partial meniscectomy	170 (76.9%)
Meniscal repair	13 (5.9%)
All-inside	11
Inside-out	2
Chondroplasty	19 (8.6%)
Loose body removal	14 (6.3%)
Debridement	5 (2.3%)
Initial opioid prescription	
Hydrocodone	214 (96.8%)
Oxycodone	2 (0.9%)
Tramadol	2 (0.9%)
Codeine	3 (1.4%)
Initial prescription size	
20 pills	68 (30.8%)
30 pills	5 (2.3%)
40 pills	98 (44.3%)
50 pills	41 (18.6%)
60 pills	9 (4.1%)
NSAID prescription	
Yes	132 (59.7%)
No	89 (40.3%)
Local anesthetic use	
Portals only	98 (44.3%)
Intra-articular	123 (55.7%)
Regional anesthesia block	
None	218 (98.6%)
Single shot block	1 (0.5%)
Continuous catheter	2 (0.9%)

*The values are given as the number of patients, with the percentage in parentheses.

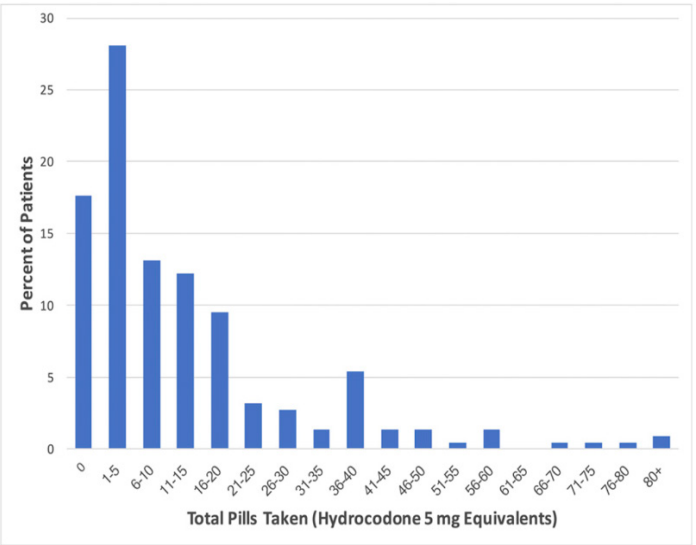


Figure 1. Distribution of total postoperative opioid consumption at time of final follow up (converted to Hydrocodone 5 mg equivalents)

TABLE III Distribution of Total Opioid Consumption (Hydrocodone 5-mg Equivalents)

No. of Pills Taken	Percentage	Cumulative Percentage
0	17.6	17.6
1 to 5	28.1	45.7
6 to 10	13.1	58.8
11 to 15	12.2	71.0
16 to 20	9.5	80.5
21 to 25	3.2	83.7
26 to 30	2.7	86.4
31 to 35	1.4	87.8
36 to 40	5.4	93.2
41 to 45	1.4	94.6
46 to 50	1.4	95.9
51 to 55	0.5	96.4
56 to 60	1.4	97.7
61 to 65	0.0	97.7
66 to 70	0.5	98.2
71 to 75	0.5	98.6
76 to 80	0.5	99.1
>80	0.9	100.0

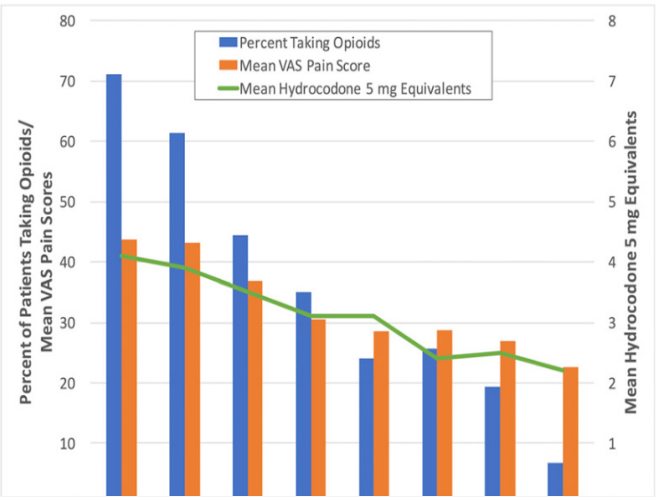


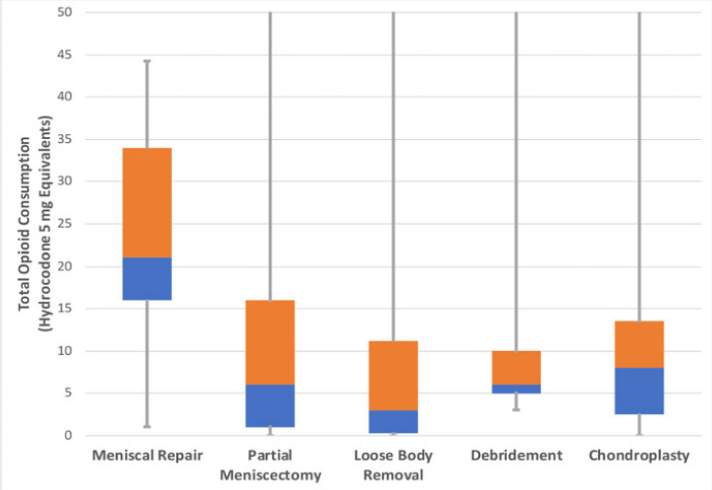
Figure 2. Percentage of patients taking opioids, mean VAS pain score, and mean opioid consumption for each postoperative day (POD). POV= Postoperative Visit

consumption, psychiatric medication usage, pre-operative pain severity or duration, PROMIS scores, Connor-Davidson resilience score, post-operative NSAID prescription and total opioid consumption. For a range of hypothetical initial prescription sizes, we calculated the percentage of patients that would have required an opioid refill and the average number of surplus pills (Fig. 4). For example, if all patients were given an initial prescription of 30 pills, approximately 15% would require a refill but the average patient would have 20 surplus pills.

Discussion

Opioid consumption after knee arthroscopy is low with nearly 50% of patients taking 5 or fewer pills and 80% taking 20 or fewer pills . More than half of patients had discontinued opioid use by third day post-op. Nearly 90% of patients reported surplus prescription medication and only half of the patients completed their initial prescription sought a refill. All this suggests that patients may consume less opioid medication than they are prescribed and for a shorter duration than expected.

Larger prescription sizes decrease the percentage of patients requiring refills but lead to increased amounts of surplus. Routine prescriptions in excess of 30 pills are unnecessary and a smaller amount (15-20) is preferable. Further, results show that while smaller prescription sizes increase refill



Figue 3. Box and whisker plot showing lower quartile, mean, upper quartile, and maximum total opioid consumption for each surgical procedure.

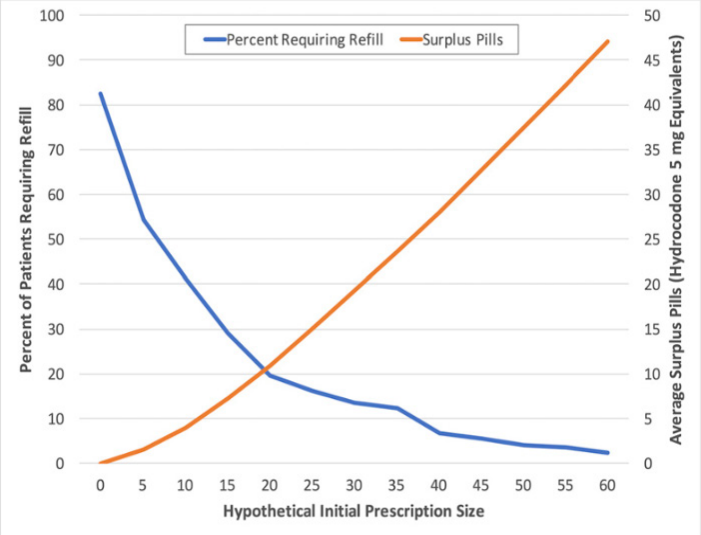


Figure 4. Percentage of patients who would require a refill and the mean surplus of pills, per initial prescription size.

requests it does not negatively impact patient satisfaction. Thus, a smaller initial prescription size could potentially require the surgeon to refill the prescription but with the benefit of reducing the amount of surplus.

Interestingly, we noticed a trend towards higher levels of opioid consumption with larger initial prescriptions with no change in patient satisfaction. There is no suspected bias as each surgeon prescribed a standard number of pills and did not tailor the prescription size to the procedure. From this we hypothesize that the initial prescription size may unintentionally set an expectation (by both the patient and surgeon) for the severity of post-operative pain and influence opioid consumption. This important finding requires further research.

We did not observe an association between psychiatric mediation usage, PROMIS scores, or Connor-Davidson resilience scale scores and opioid consumption. This is in contrast to Helmerhorst and colleagues ; whose study found that patients who scored higher on catastrophic thinking, anxiety, and depression questionnaires were significantly more likely to take opioid medication one to two months after surgery for orthopaedic trauma regardless of injury severity, fracture location, or treating surgeon.5 This may be explained by the difference in the experience of trauma surgery versus elective knee surgery, as well as the demographics of the typical patient for each situation.

A few limitations to this study should be noted. First, patients were not blinded to their participation or the study aims and may have reduced their opioid consumption. In an attempt to counter this, surgeons were excluded from data collection or pill counting. Second, we were unable to account for opioid prescriptions that patients may have obtained from other providers. Despite our best efforts, this may have introduced a bias favoring lower opioid consumption. Selection bias of patients who agreed to study participation may have influenced our results if these patients differed systematically from those who declined enrollment. Additionally, the suburban location created a bias so that the study population did not have many people from a low socioeconomic background or underinsured, which are groups known to require higher numbers of opioids after orthopaedic procedures.

Physicians are put in a difficult position between their responsibilities to society and their expectations to manage the pain of their patients. The results of this study can help to establish a protocol for knee arthroscopy related opioid prescriptions in hope of reducing this incongruity- to minimize pain as well as the amount of excess opioid medication.

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Gription Porous-Coated Acetabular Cup in Total Hip Arthroplasty (THA): A Review

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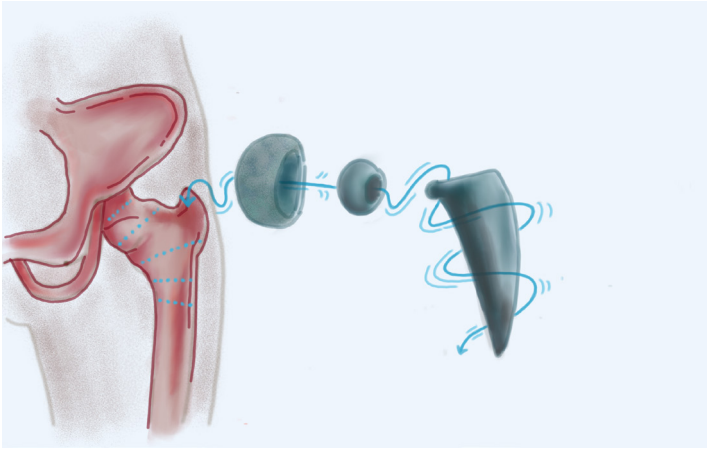

Art by Niko Morozov

Total hip arthroplasty (THA) is one of the most successful procedures performed worldwide. With more than one million of these procedures performed annually, THA relieves pain, restores joint function and improves the patient's overall quality of life. 1,2 As a result of increased demand for this procedure, the increase in life expectancy,and the consideration that some patients may require a revision surgery in the future, surgeons are faced with an array of challenges. 3

One the biggest challenges surgeons face in revision of THA is acetabular reconstruction with bone loss. Bone loss challenges the surgeons' ability to provide enough surface area for bony ingrowth. 4 One of the major contributors to the management of bone deficiency is the make-up of the prosthetic acetabular cup. Traditionally, the management of bone deficiency involved reconstruction with acetabular structural allografts protected by a cage. However, these components are limited due to concerns over biological fixation and implant failure. As a result, data has recently accumulated in support of using a porous tantalum coating as an alternative. 5–7

It is known that a porous coating on acetabular cups improves bone in-growth and lowers the incidence of aseptic loosening. As the porous surface on the coating is biocompatible with osteoblasts, it is thought that this promotes osseointegration. 8

The Gription cup is a recently released ultra-porous product designed to provide an advantage in promoting bone in-growth and improve procedural outcomes, compared with other available coatings.

Built on the foundations of POROCOAT porous coating – a product supported by medical literature with more than 30 years of clinical experience—Gription emulates some of its proven and heavily researched clinical advantages. Gription is unique from its contemporaries in that it offers a uniquely high coefficient of friction, high gradient volume porosity and optimal pore size. Despite an upgrade in these parameters, little is known if this product can improve post-operative clinical outcomes.8

The rationale behind these ultra-porous implants is that they are designed to improve osseointegration. In order for there to be good osseointegration, there must be sufficient primary stability at the bone-implant interface. Beckmann et al. 9 compared 2 revision cups with the same geometry but different surface compositions: a highly porous titanium surface and the conventional sintered-bead surface. They concluded that there was no substantial difference in the primary stability at the bone-implant interface between the newly porous cups versus the conventional sintered-beaded cups.

In another study, Beckmann et al. 10 investigated whether a highly porous Gription acetabular cup (GAC) provides greater stability than the conventionally used POROCOAT acetabular cup (PAC) for high-grade acetabular defects. They used relative motion as an index for primary stability and osseointegration. In order for successful osseointegration to occur, there must be minimal relative motion between the implant and the bone. In cases with low bone mineral density, the conventional PAC displayed less relative motion than the ultra-porous GAC indicating a greater osseointegration than the porous cup. Suggested in their findings was that at low bone

mineral density, the newly ultra-porous GAC in fact provides worse stability and is therefore less advantageous than the conventional sintered-bead PAC.

One of the unique clinical advantages Gription offers over its counterparts is one of the industry's highest coefficient of friction. It is argued that increasing the surface roughness improves the initial fixation between the implant and the bone 11. Goldman et al. 12 set out to discover whether a cup with a higher coefficient of friction actually increased stability at the bone-implant interface. They found that when isolated for a high coefficient of friction, as provided by Gription, there was no advantage in stability compared with its counterpart. This does not support the hypothesis that Gription's uniquely high coefficient of friction aids in implant stability and osseointegration.

Although research has demonstrated that a high coefficient of friction, a highly porous volume and optimal pore size all serve to improve osseointegration and joint stability, there is little research that shows Gription offers any clinical advantage over its contemporaries. Furthermore, a concerning report by Carli et al. 13 found that the ultra-porous Tritanium cups in fact demonstrated inferior radiographic findings compared to their contemporary Trident cups. Given that Gription is a relatively new product, little research has been done to evaluate the effectiveness of the ultra-porous implant, especially in the long term. It offers unique features that exhibit promising clinical implications, but future studies presenting mid and long-term outcomes are necessary in order to assess whether this product can be implemented across departments worldwide.

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Determining Optimal Dose of Clinical Grade Progenitors for Photoreceptor Preservation in Rodent Model of Retinal Degeneration

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Abstract

Retinitis pigmentosa (RP) and age-related macular degeneration (AMD) are devastating conditions with limited treatment options that are the major causes of blindness worldwide[1]. Stem cell therapy offers to slow down disease progression2. Previous studies have shown that neural progenitor cells preserve photoreceptors and visual function following subretinal injection into Royal College of Surgeons (RCS) rats, a well-established rodent model with a MERTK gene mutation for retinal degeneration3. Our goal for this study was to determine the optimal dose for photoreceptor preservation without adverse effects (i.e. tumor formation). This will allow further development in ocular regenerative therapies, with potential to revolutionize the approach to retinal diseases. Experiments were performed by injecting 6k, 60k, or 400k clinical grade hNPCs into the subretinal space of RCS rats at postnatal day 21-23, or at the onset of retinal degeneration. Non-invasive spectral dominant optical coherence tomography (SD-OCT) was performed to monitor graft distribution and photoreceptor preservation. Optokinetic response (OKR) tested visual function and histological examination of donor cell distribution and photoreceptor preservation were performed after clinical evaluations. During histological and SD-OCT examinations, the grafted donor cells redistributed into the subretinal space, starting with a lump of cells at the site of injection and spreading to a layer of cells. Clinical examination revealed that 60k and 400k/injection offered greater visual acuity compared with 6K. 60k was the optimal dose for subretinal injection in RCS rats. These results validated the efficacy of human neural progenitor cells (hNPCs) produced under good manufacturing practice (GMP) conditions following subretinal injection into the RCS rats.

Introduction

Retinal degenerative diseases (RDDs), such as RP and AMD, are characterized by progressive loss of photoreceptors. RDDs have multifactorial causes, which complicate diagnostic and treatment measures. RP is known to have more than 70 mutated genes that cause abnormalities in photoreceptors, leading to vision loss (4). For example, MERTK gene mutation reduces retinal cells to carry out many physiological processes, such as cell survival, migration, differentiation, and phagocytosis of apoptotic cells, which results in their degeneration and loss of vision3. RP may occur sporadically or as part of a syndrome, and may be inherited in a dominant, recessive, or X-linked manner3. Furthermore, several life-style and dietary measures have been linked to AMD-type vision loss5,6. Damage to photoreceptors in AMD is attributed to the accumulation of reactive

Art by Olivia Keller-Baruch

oxygen species and peroxide and chronic inflammation in the retina6. Unfortunately, no treatments are currently available for most RDDs.

Among ongoing research efforts to develop advanced treatment strategies, stem cell-based therapies hold great potential for the rescue and/or prevention of many diseases, such as vision loss in RDDs. Stem-cell therapy is a relatively new approach2. Known therapeutic strategies for RDDs use stem-cell neuronal cells to replace host degenerated photoreceptors of the retina, to promote trophic factor secretion that enables survival of existing cells; or to act in a neurosupportive role, which slow the

progression of degeneration and help retain visual function1. Among many types of stem cells, hNPCs have been exemplified long-term neuroprotection and preservation of visual function in a rat model of photoreceptor degeneration3.

MERTK gene mutations in RCS rats have been identified in a subset of patients diagnosed with retinitis pigmentosa7. The use of RCS rats served as a clinically relevant model for this study. Previous studies presented that the use of hNPCs stops or slows the progression of photoreceptor degeneration and visual function in RCS rats3. Bharti et al. and Mead et al. demonstrated that approximately 60,000 stem-cell derived retinal pigmented epithelial cells (RPE) are required to cover the macular region to restore RPE-mediated recycling of photoreceptor segments9,10. With these studies in mind, we aimed to determine the optimal dose of progenitors for photoreceptor preservation in RCS rats by injecting three different doses of 6k, 60k, and 400k of clinical grade hNPCs into the subretinal space. We hypothesized that 60k hNPCs would be the optimal dose at which to preserve photoreceptors in RCS rats.

Methods

Clinical grade hNPCs were injected into the subretina of the right eye of the following groups (G): G1 (n=7) transplantation medium; G2 (n=8) 6k cells, G3 (n=8) 60k cells, and G4 (n=8) 400k cells. All left eyes were untreated, providing us with our control group. After the surgical injection, rodents received daily administrations of oral cyclosporine A to prevent immune rejection.

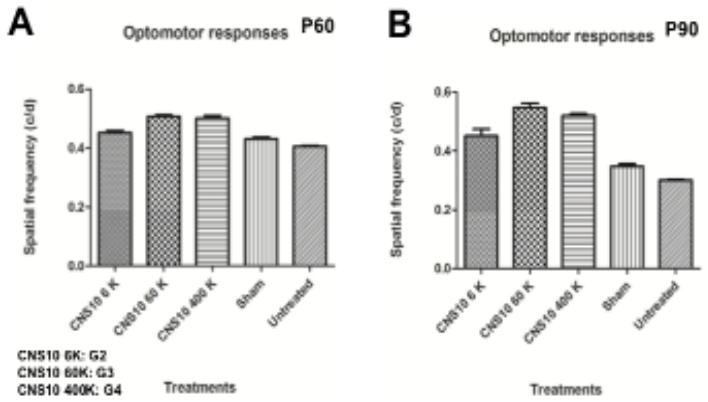

Figure 2. Visual acuity measured by optokinetic response (OKR).

SD-OCT is a non-invasive imaging technique that uses light waves to capture cross sections of the retina, allowing us to observe donor cell distribution and retinal lamination. Optokinetic response (OKR) was performed to measure visual acuity of animals (Figure 1C). Histologic study was performed after clinical examinations. Cryostat sections were stained with cresyl violet to evaluate overall retinal lamination; selected sections were also stained with human specific antibodies to identify donor cell survival and distribution. The lengths of ONL were measured with ImageJ. The percentage of ONL rescue for each group was quantified for statistical difference.

Results

The OKR determines the spatial frequency threshold and constitutes one possibility to measure visual acuity. The visual acuity of the rodents at P60 present an average of 0.44 cycles per degree (c/d) in 6k, 0.52 c/d in 60k, 0.51 c/d in 400k, and 0.42 c/d in the sham group (see figure 2A). The OKR showed

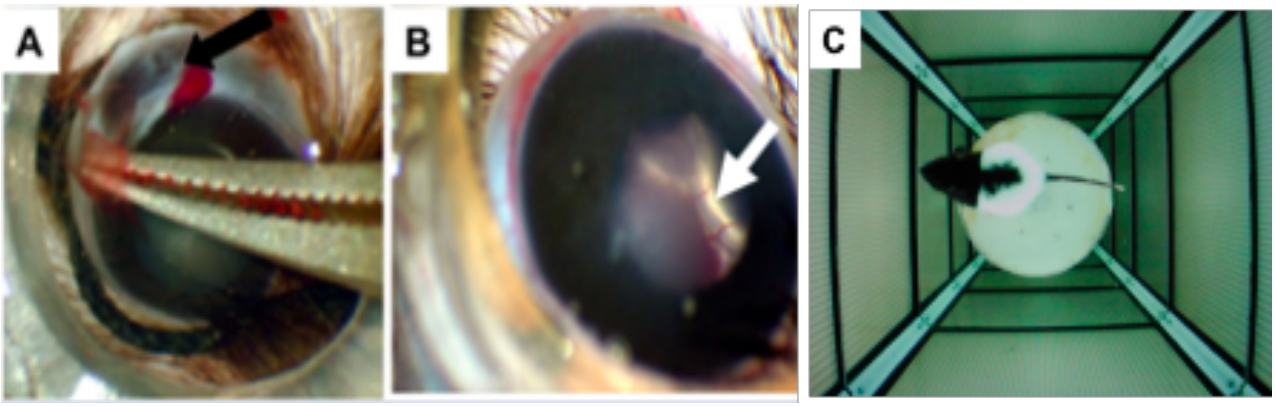

Figure 1. (A) Arrow shows a trans-scleral injection site to access subretinal space. (B) A successful subretinal injection examined under surgical microscope. The subretinal bleb (white arrow) was created from the injection. Retinal blood vessels above the bleb indicate the injection was in the subretinal space.

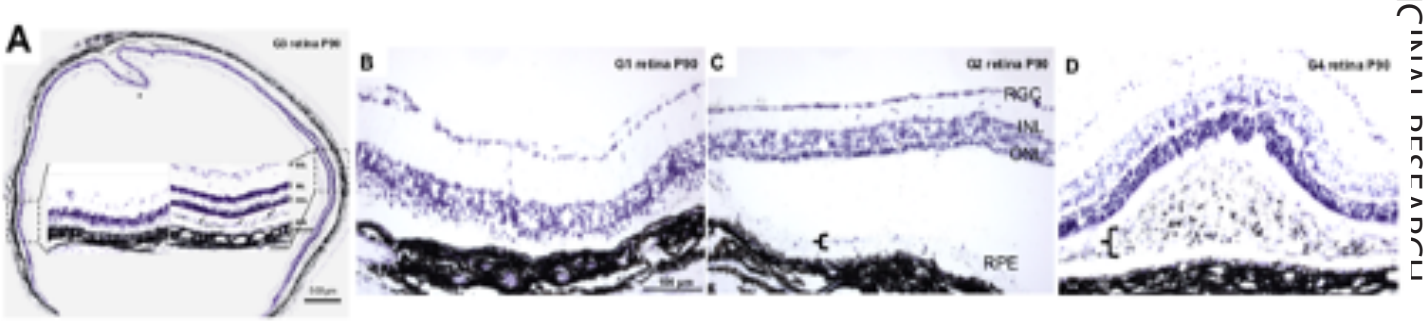

Figure 3. Progenitor cells preserve photoreceptors. (A) G3,CNS10- 60K shows preservation of ONL, right panel compared to untreated control, left panel; arrows shows grafted hNPCs. (B) G1, control medium, 1-2 cell layer of ONL with damaged RPE. (C) G2, CNS10 6K, 3-4 cell layer of ONL. (D) G4, CNS10-400K, 5-8 cell layer of ONL. Brackets in C and D indicate grafted progenitor cells in subretinal space. Folds in retina due to processing.

that all values at P60 are significant except comparing 6k with sham, and 60k with 400k ($P<0.05$).The visual acuity of the rodents at P90 present an average of 0.44 cycles per degree (c/d) in the 6k, 0.55 c/d in the 60k, 0.53 c/d in the 400k, and 0.32 c/d in the sham group (see figure 2b). All values at P90 were significant except comparing 60k with 400k ($P<0.05$). Results at P90 were similar to the results at P60 but with greater magnitude, indicating visual acuity was maintained unchanged with time. 400k injection did not offer greater visual acuity compared with 60k in P60 nor P90 ($P>0.05$).

Retinal section montage image presented overall outer nuclear layer (ONL) preservation and donor cell distribution (Figure 3). The ONL of photoreceptor nuclei was significantly thicker in regions containing grafted cells (8 cell layers) than in regions distal to the graft (1-2 cell layers). RPE integrity was preserved at graft sites (pigmented black cell layer in the subretinal space by melanin). Neural retina displacement was not observed by P90 in 60k injected eyes (Figure 3A). ONL is 1-2 cell layer thick and RPE showed damage in control G1, medium-injected eyes (Figure 2B). In G2, 6K-injected group, ONL is 3-4 cell layer thick (Figure 3C). ONL is 5-8 cells thick in G4, 400K-injected, group (Figure 3D); however, a large lump of cells was observed in 400k, compared to 60k group where the grafted cells spread for long distances in the subretinal space (Figure 3A).

The OCT demonstrated that ONL was much thinner in untreated and G1/control RCS rats (Figure 4B-D) than wild type due to degeneration (Figure 4A). The G2/6K group showed the same ONL thickness as the control G1/control group (Figure 4E&F). However, 60k- and 400k-injected groups (Figure 4G-J) showed much thicker ONL compared to G1/control group (Figure 4C&D) and G2/6K group (Figure 4E&F). Subretinal blebs (injected cells) were present at both P60 and P90 with high dose (400K) injection, indicating that the graft did not spread through subretinal space (Figure I&J). Retinal histological examination of the G4/400K group also showed a large lump of cells in the subretinal space (Figure 3D). Overall, OCT imaging correlated with retinal histology.

The percentage of preserved ONL was measured against the whole retinal length on retinal

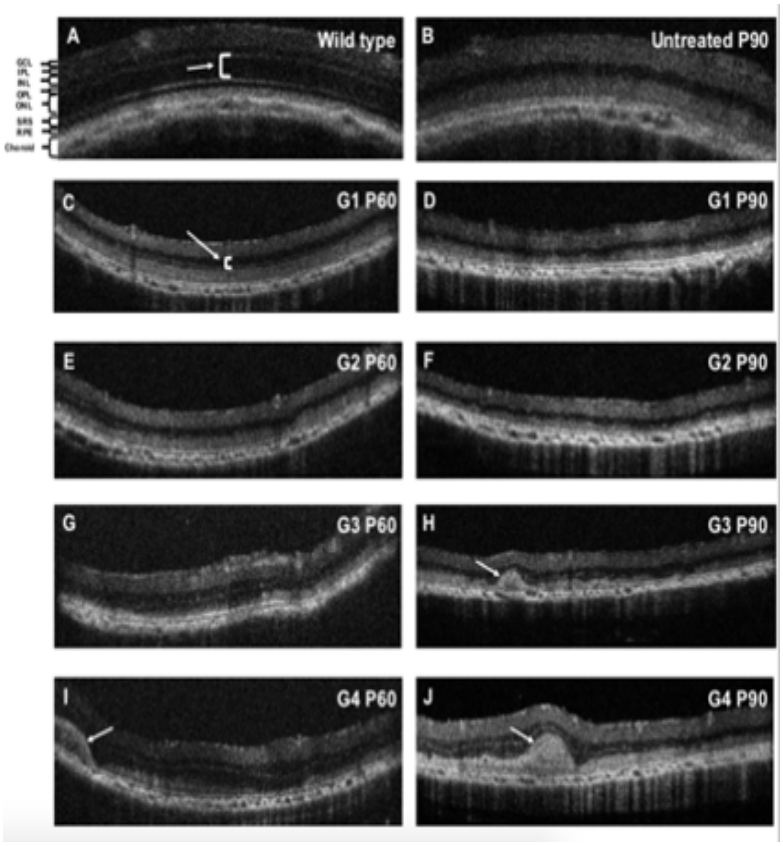

Figure 4. Optical coherence tomography (OCT) showing donor cell distribution and retinal lamination. Brackets indicate ONL.

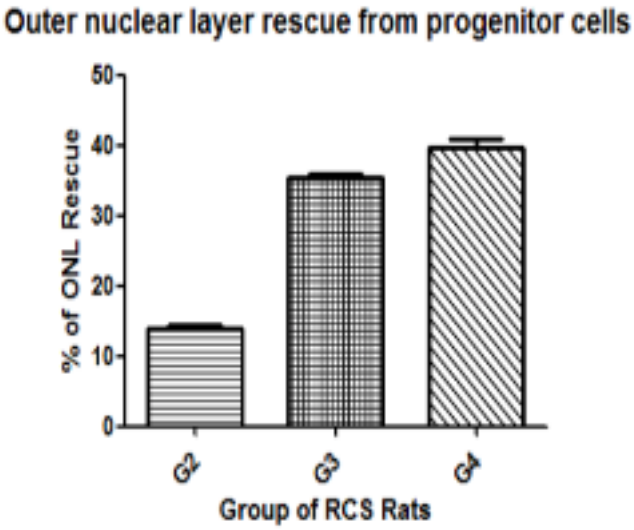

Figure 5. Dose escalation correlates with preserved outer nuclear layer (ONL).

sections. The percentage of ONL rescue was 13% in 6k, 37% in 60k, and 39% in the 400k group (figure 5). The 60k group had significantly larger ONL lengths than the 6k dose and transplantation medium ($P<0.05$). All data was collected at P90.

Grafted progenitors remained as neural progenitors as revealed by Nestin-positive staining after being grafted into the subretinal space of RCS rats (Figure 6).

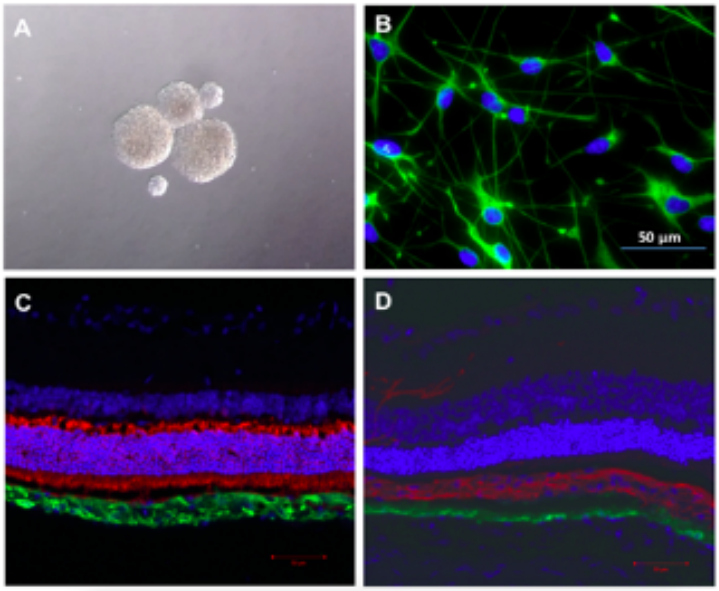

Figure 6. Clinical grade neural progenitor cells remain as neural progenitors in vitro and in vivo. (A) The progenitors grow as spheres. (B) Antibodies Nestin-positive progenitor cells in green. (C&D) Recoverin in red and Nestin in green in RPE 65 antibody staining.

Discussion

Establishing the dosage of stem cell transplantation is a critical part of advancing into the clinical phase of effective treatment with minimum side effects. About 60,000 stem cell-derived RPE cells are required to cover the macular region to restore RPE-mediated recycling of photoreceptor segments8,9. Therefore, 60k was one of our hNPC-injected doses in addition to 6k and 400k. The OKR results showed that there was a significant difference in spatial frequency between the 6k and 60k in both P60 and P90. However, there was no significant difference between the 60k and 400k. Thus, the 60k hNPC was the optimal dose in improving visual acuity. The retinal section montage and OCT also showed that the 6k dose presented a significant decrease in ONL rescue percentage compared to the 60k dose, while there were no differences between the 60k and 400k dose in ONL rescue. Thus, the 60k hNPC was also the optimal dose in preserving the ONL and distributing the donor cells. A limitation to this study may have been the lack of dosages in between 6k and 60k hNPC in order to see if the usage of less neural progenitor cells may have the same effect as 60k and 400k. To further enhance the reliability of the results, a larger sample size could have been utilized. Presently, the development and optimizing of stem cell-based treatment make a turning point in medicine.

Due to the lack of current treatment of RDDs, neural progenitor cells create hope for the blindness.

Conclusion

Clinical grade hNPCs offer preservation of both photoreceptors and visual function following subretinal injection into a rodent model for retinal degeneration. Our clinical grade hNPCs remain as neural progenitors in vitro and in vivo (Figure 6), which may explain their long-term effects in rescuing vision loss. These conclusions validated previous studies with research grade hNPCs tested in the

same animal model3. Grafted donor cells survived and distributed in the subretinal space as a lump of cells initially, then spread into layers. Our study showed that 60k hNPC-injected eyes had the best acuity vision and ONL rescue compared to control, 6k and 400k, which was confirmed by several techniques including OKR, OCT and histological examination (Figures 2-4). The high dose of 400k did not offer additional benefit over the 60K dose in terms of visual acuity preservation. Therefore, 60k was the optimal dose. Correlated with functional data, histological examination and OCT showed that the percentage of preserved photoreceptors over the whole retinal length on retinal sections was significantly larger in the 60k group compared with other groups. Further, grafts migrate long distances in the 60K group, while a big lump of cells was observed in the 400k group. No doses showed tumor formation or any unwanted pathology. Preclinical animal studies are essential in providing both safety and efficacy of treatments before proceeding to human clinical studies. Further preclinical trials should be done on larger animal models such as pigs that have more similarity in organ size to humans. A new optimal dose should be assessed. By doing so, this will allow us to step closer to a successful translation of treatment to the clinic.

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