

***Traditional Intravenous Fluid versus Oral Fluid Administration in Primary
Total Knee Arthroplasty: A Randomized Trial***

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1. Purpose: Evidence-based guidelines on optimal perioperative fluid management have not been established in patients undergoing orthopaedic surgery. Typical intraoperative and post-operative fluid management has been arbitrary without evidence based guidelines established following total joint replacement. We have observed many patients post-operatively with side effects such as fluid overload leading to medical complications requiring either prolonged hospitalization or readmission. Additionally, this overload may lead to wound healing complications secondary to fluid shifts which may be devastating in this patient population. Recent randomized trials in major abdominal surgery suggest that large amounts of IV fluid may increase morbidity and hospital stay. Additionally, this increase fluid may be detrimental in patients with anastomosis leading to failure and/or complications in this patient population. We have defined to specific groups of interest to study in this patient population with regards to fluid management. The first group is the “traditional” IV fluid group where the anesthesiologist gives an unspecific amount of fluid intraoperatively and post-operatively the patient gets a set amount of fluid based on “protocol” on the orthopaedic floor (i.e. 75 cc/hour until good oral intake). This is the protocol utilized by most orthopaedic practices throughout the United States. The second group is defined as patients who are given a specific protocol preoperatively to optimize hydration, followed by limited fluids intraoperatively based on physiologic parameters. This study will investigate the effects of two regimens of intraoperative fluid management (“traditional” vs. “oral”) with physiologic and patient function as primary outcome measures after surgery.

2. Procedures:

- Patients meeting the inclusion criteria who are schedule for unilateral primary TKA will be identified.
- The patients will be approached regarding the study (in clinic by research staff) and if the patient is agreeable, informed consent will be obtained.
- The patients will be randomized into the traditional vs. oral treatment groups (see below for details and protocol). The protocol for each group will be placed in sealed envelopes, 65 for each group, and picked randomly for each patient.
- The patients will attend their normal preoperative visits with the surgical team as well as their regularly scheduled preoperative clearance visit with the medical doctor (Surgery Welcome Center)
- Standard preoperative labs will be obtained (hematocrit, basic metabolic panel), at their preoperative appointment
- Additional preoperative labs will include urine specific gravity to monitor patient hydration which will be obtained the morning of surgery; this will be paid for by the CJR research fund.
- Standard laboratory values (hematocrit and basic metabolic panel) will be obtained postoperative day #1 and #2, if the patient has not been discharged.
- Urine output will be monitored on postoperative day #1 and #2 which is standard protocol
- Additional test will include urine specific gravity on postoperative day #1 and #2 as a marker of hydration as long as the patient is still in the hospital. If the patient is discharged postoperative day #1 we will collect this once in the morning, and once more before they are discharged. Payment of the cost of these laboratory evaluations will come from CJR research funds.
- Patients are encouraged to attend physical therapy 2-3 times a week for 6 weeks. Physical therapy log is attached with ROM and Girth measurement collected once a week for 4 weeks.
- Hematocrit, basic metabolic panel and urine specific gravity 2 weeks postoperatively at their routine follow-up visit will also be obtained. The cost of these laboratory tests will come from CJR research funding.
- Sixty-five patients in each group will be recruited for this study (see stats for power analysis). We will increase our number of enrollment to 75 in each group to account for patients that drop out and withdrawals from the study.

Traditional Fluid Protocol

- NPO Clears and Food after midnight.
- 2 Liters of lactated ringers administered by anesthesia intraoperatively.
- Postoperatively - 2 Liters of Crystalloid while in PACU and Inpatient Room for a Total of 4 Liters of Crystalloid within 24 hours.
 - Patient will receive 500 milliliters while in PACU and 1500 milliliters while in their Inpatient Room, for a total of 2 Liters.
- Spinal drug choice standardized: 9 mg (1.2 ml) –11.25 mg (1.5ml) of Spinal Bupivacaine 0.75%with Dextrose 8.25%. We have also attached the spinal anesthesia guidelines that will be followed for this study (see attached).
- Ondansetron 4mg IV given prior to regional anesthesia; repeat x 1 prior to the end of surgery.
- Ultrasound Guided Adductor Canal Block using 30 ml of Ropivacaine 0.35% Preservative Free.
- Normal diet postoperatively.

Oral Fluid Protocol

- Patients encouraged to drink a minimum of three, 20 ounce cups of clear liquid per day each day for the 3 days prior to procedure. Examples of clear liquids include water, clear sports drinks, fruit juices without pulp. Please limit caffeinated and carbonated beverages to no more than 1 drink per day.
- NPO Food/Milk: none beginning 8 hours prior to procedure time.
- NPO Clear Liquids — Patients are asked to drink 10 ounces of clear liquid 4 hours prior to their scheduled procedure time.
- In the preoperative holding area, an IV is started in the patient; and the patient is given Lactated Ringers IV fluid at a rate of 75ml/hr. The IV fluids will be stopped and the IV hep-locked in the PACU when the patient is taking PO fluid; the total amount of IV fluids given to the patient is charted and is not to exceed 500ml total.
- Spinal drug choice standardized: 9mg (1.2 ml) -11.25(1.5ml) mg of Spinal Bupivacaine 0.75%with Dextrose 8.25%.
- Ondansetron 4mg IV given prior to regional anesthesia; repeat x 1 prior to the end of surgery
- Ultrasound Guided Adductor Canal Block using 30 ml of Ropivacaine 0.35% Preservative Free. Normal diet postoperatively.
- PO fluid protocol implemented on the floor immediately postop: a minimum of three, 20 ounces cups of liquid per day for 3 days. Patients can drink more than the minimum if they feel dehydrated.

Primary Outcomes

A. Body Weight – scales will be purchased and provided to the patient while participating in the study. All weights will be obtained on the same scale for each patient to assure consistency of measurements. Measurements will be performed in the preoperative holding area prior to surgery, the evening of surgery on the orthopaedic floor and every morning the patient is hospitalized using the same scale assigned to that patient. Body weight measurements will be repeated at home 48 hours' post-discharge and at one and two weeks either at home or in the clinic with the same scale as previously utilized. An additional measurement will be obtained at 3 weeks postoperatively if the patient's body weight at 2 weeks has changed more than +/- 2% from their preoperative value. Funding of the cost of the scales will come out of the CJR research funding.

B. Knee Range of Motion: This will be assessed preoperatively (at their clinic appointment), on POD #1 and 2 by the research staff if the patient has not been discharged, and at 1, 2, 3 and 4 weeks postoperatively by the outpatient physical therapy office. Patient standardized forms will be provided to the outpatient physical therapists to record all post-hospital measurements. Measurements will be done with a standard goniometer.

C. Leg Anthropometric (Girth) Measurements: girth measurements will be performed at 5 & 10 cm suprapatellar, midpatella, and 10 cm infrapatellar with the use of a standard tape measure. These measurements will be collected at their pre-operative visit by research staff, POD 1 and 2 by research staff, if the patient has not been discharged and post-discharge measurements will be performed by the outpatient physical therapist at the same intervals and recorded on the same outpatient data sheet as described in item B above.

D. Transfusion: Number of transfusions will be recorded and compared between both groups. Transfusion criteria will not deviate from our normal post-operative care protocol.

E. Wound Complications: the incidence of wound infection and wound drainage will be assessed and recorded. Compressive dressings will be changed daily until wound is dry. If wound is draining at hospital discharge, the patient will be provided with home dressing supplies and instructed on how to perform daily dressing changes. The patient will take a daily photo of the wound and removed dressing daily and email it to CJR until the wound is dry. This is standard protocol for our patients currently.

F. Thromboembolic Disease: Screening will be based on clinical assessment of the participating medical team members, which is standard protocol with all of our patients. The incidence of thromboembolic events will be recorded. All patients in the study will use aspirin 81 mg twice daily for DVT prophylaxis.

G. Muscle Strength: quadriceps strength will be assessed on POD #1 and 2 by research staff (in the hospital) and repeated at 2 and 6 weeks postoperatively at their standard of care follow-ups in the office by research staff. The strength testing will be calculated using a handheld dynamometer which is standard testing for strength in many post-operative patients currently.

H. Functional Performance Assessment: Functional tests will be performed at their preoperative appointment and once again at their 2 and 6 weeks postoperatively and will include the timed up and go (TUG) and the 30 second sit-to-stand tests. The tests will be performed in the office by research staff. These are standard tests that are often performed in physical therapy clinics to assess patient progress.

I. Length of the Hospitalization & Readmission Incidence will be recorded for both groups.

J. Postoperative Pain Assessment: Pain will be assessed using a pain VAS scale daily while hospitalized, then three times per day for 4 weeks postoperatively. Patients will be given a log to record these measurements outside of the hospital setting.

K. Adverse Events: episodes such as symptomatic hypotension (light-headedness, syncope), emesis, the need the IV fluid boluses, and other hospital and post-discharge events will be recorded.

L. Blood Pressure: this will be recorded in the Preoperative Care Unit, PACU, upon arrival to the nursing unit, and every 8 hours thereafter while hospitalized. This is standard practice for all of our patients currently.

M. PONV (Post-operative Nausea and Vomiting) - PONV will be assessed throughout their hospital stay; vital signs are checked per hospital nursing protocol, patients will be asked about Nausea: None, Mild, Moderate or Severe.

N. Patient Reported Outcome – We will be collecting the Knee Society Score(KSS) Knee injury and Osteoarthritis Outcome Score (KOOS) and the VR-12 from the patients pre-operatively as well as at their 2 week and 6 week follow up appointments. These are validated patient reported outcome measures that are already collected as standard of care at Colorado Joint Replacement.

O. Pressors – We will be collection the total amount of any pressor drugs (e.g. Ephedrine and Phenylephrine) given intra-operatively and in PACU in both groups.

P. Oral Fluid Intake Log – The patients that are in the Oral group will have an additional page to keep track of their fluid intake prior to surgery.

Q. Bioimpedance machine - This will be used to track patients body composition before and after surgery. Research staff in the office will collect this information at the patient's pre-op visit, POD#1 and 2 as well as their 2 week and 6 week visit.

R. Body Temp – The patient's body temp will be recorded pre-operatively as well as in the recovery room.

S. Time from their last clear fluid drink to the start of anesthesia, this start up time will be recorded for both groups.

T. Patient perception/satisfaction with their fluid protocol.

Patient Withdrawal: subjects may withdraw from the study for any reason at any time. Should a subject decide to withdraw from the study, all data collected up to that point will be deleted and not used for statistical analysis. Withdrawal from the study will not affect the patient's treatment after their total knee arthroplasty.

3. Scientific Background of the Study – As stated in the “purpose” section –

Evidence-based guidelines on optimal perioperative fluid management have not been established in patients undergoing orthopaedic surgery. Recent randomized trials in major abdominal surgery suggest that large amounts of fluid may increase morbidity and hospital stay. This study will investigate the effects of two regimens of intraoperative fluid management (“traditional” vs. “oral”) with physiologic and patient function as primary outcome measures after surgery.

4. Specific Aims of the Study – This study will investigate the effects of two regimens of intraoperative fluid management (“traditional” vs. “oral”) with physiologic and patient function as primary outcome measures after surgery.

5. Description of risks and measures to minimize risks.

- All patients, regardless of their volume protocol (traditional vs. oral), will follow a traditional post-operative course which includes daily labs and monitoring physiologic status from both the orthopaedic and general medicine team.
- All patients will have traditional post-operative follow-up care which will not be varied.

Surgical Risks:

There are risks and complications that are associated with all artificial knee surgeries. These have all been discussed with you by your surgeon's team prior to surgery. You are at no increased risk of known complications in this study.

Testing Session Risks:

Though the procedures that you will be exposed to are safe, discomforts you may experience while in this study include:

- Commonly - muscle soreness after muscle strength testing for approximately 2 days after testing. This soreness is similar to the muscle soreness that you may feel if you lift weights or vigorously exercise after a long time off
- Less commonly – muscle strains or tears

The study may also include risks that are unknown at this time.

The investigators have a data safety monitoring plan (DSMP) that includes the Principal Investigator monitoring confidentiality, protection of subject privacy, database protection, confidentiality during adverse event reporting, adverse event information including definitions of adverse events, classification of adverse event severity, adverse event attribution scale, expected risks, adverse event reporting and follow-up, serious adverse event reporting, data quality and management, participant accrual and compliance, measurement and reporting of participant adherence to protocol, designation of an independent physician, informed consent process, and reporting change in study status. In addition, to monitor the safety of the subjects enrolled every quarter an independent physician will review the studies adverse events as well as inclusion/exclusion to ensure there is no increased risk to subjects who are taking part in the study. Study staff will ensure that the IRB is informed in a timely manner of any recommendations, decisions, findings, actions, or steps mandated by the DSMP.

6. Benefits to subjects and/or society.

- Other studies (non-orthopaedic) have shown benefits with wound healing and a potential decrease in adverse events after abdominal surgical procedures. It is unknown if there will be a difference between the two protocols in our study. The potential benefits to the oral group include decreased wound complications, improved functional outcomes and the potential for a decrease in healthcare expenditure per surgery.

Patient Selection Criteria

INCLUSION

- Patients between the ages of 18-75 years old undergoing a primary total knee arthroplasty for a diagnosis of degenerative osteoarthritis who do not meet the exclusion criteria listed below.

EXCLUSION – patients will be screened for the following exclusion criteria at their routine preoperative appointment with the orthopaedic and internal medicine teams.

- Volume-dependent cardiac conditions:
- Aortic stenosis
- Pulmonary valve stenosis
- Subaortic stenosis
- Severe Aortic Insufficiency
- Chronic systolic heart failure
- Eisenmeinger Syndrome
- Severe pulmonary HTN
- Chronic or paroxysmal dysrhythmias
- Pre-operative electrolyte abnormalities
- Abnormalities of the HPA (hypothalamic-pituitary axis)
- Stage 3 Chronic Kidney Disease (or worse)
- Patients taking angiotensin receptor blockers (ARB)
- Patients with uncontrolled diabetes mellitus (patient with A1C of 7+ or on insulin)
- Patients whose BMI is > 38 or < 19

- Current use of long acting narcotic medication or 3 or more months of daily short acting narcotic medication
- Patients at risk for electrolyte abnormalities, dehydration or intra-operative hypotension. (patients taking angiotensin receptor blockers, ACE inhibitors (48 hours prior to surgery) and Diuretics)
- Patients with severe, untreated or uncontrolled GERD.
- Patients that cannot receive spinal anesthesia (e.g. patient with back fusions)
- Pre-Operative Anemia (pre op HCT <30%)

7. Treatment/Intervention Schedules or in the case of observational studies:

- As per section #2

8. Data Collection Procedures

- Preoperative history and physical will be performed as usual by the surgeon and/or their physician assistant. The patient will also be evaluated preoperatively (per standard procedure) by the general medicine team as well.
- Please refer to section 2 and 8 for the outcome measures, how they will be collected and the time intervals designated.
- Data will be stored on a password protected Microsoft Excel spreadsheet on a Centura approved secure computer.
- All data collected will be de-identified.

9. Methods of Evaluation

Based on my reading of the fluid management protocol, the study evaluates the hypothesis that the euvoolemia regimen leads to better outcomes than the traditional regimen. The former corresponds to the treatment group and the latter to the control group for the analysis, and assuming that the two groups demonstrate similarities in terms of potential pre-treatment confounding variables, such as measures obtained from preoperative history and physical, a comparison of post-treatment outcomes seems appropriate (e.g., t-tests). Even under random assignment to treatment, checks can be performed to ensure effective equivalence of confounders across treatment and control groups, an essential step in the case of small samples. If the results of such checks reveal potential confounding, including control variables in the analysis may be appropriate (e.g., in a linear regression) or a matching design to generate treatment-control pairs can be used.

While I do not have any substantive training in this field, it seems that some of the outcomes listed in the Procedures: Primary Outcomes section of the protocol may be mediated by others. For example, the association between receiving the treatment and readmission or length of hospitalization may be mediated by some of the other outcomes listed. Are there any known or suspected mediators at this point, either from the list of outcomes or beyond?

Concerning statistical power, in the figure below I calculate power (y-axis) for a range of hypothesised values of estimated effect sizes (colored lines), sample sizes per treatment and control group (x-axis), and arbitrarily chosen levels of significance (α) across the panels. Regarding α , I start with 0.05 and then make an adjustment based on an arbitrary number of hypotheses to be evaluated (eight, in this demonstration). The solid horizontal line at 0.8 represents the commonly accepted power value. As an example from Figure 1(b), for a medium-high effect size of 0.6 (green line) and evaluating eight hypotheses, in order to achieve power of 0.8 would require approximately 65 participants in each of the treatment and control groups.

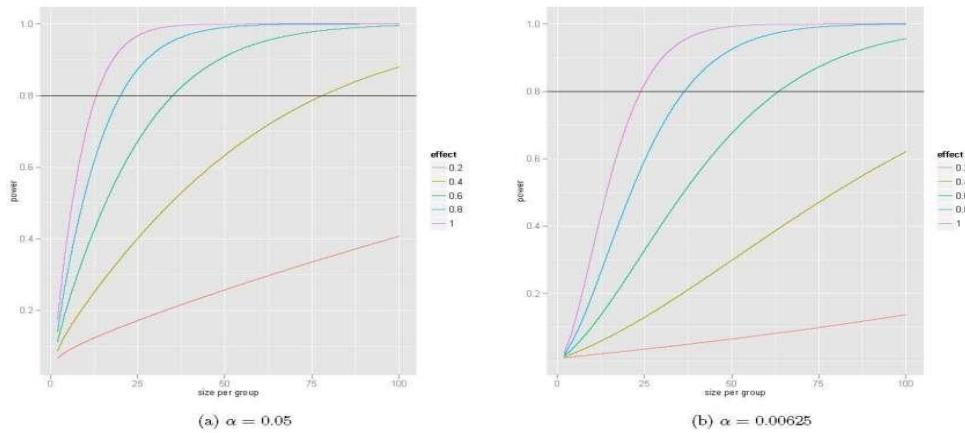


Figure 1: Power calculations for hypothetical effect sizes and sample sizes (per group) at given values of α . The left panel uses $\alpha = 0.05$ and the right panel employs a Bonferroni correction for multiple hypotheses. In this case, evaluating eight hypotheses with a desired α of 0.05 yields an adjusted α of 0.00625.

10. Trial Design

- Please refer to the above sections regarding the discussion of the research study
- Patients will be identified based on the inclusion and exclusion criteria stated above. The patients will then be randomized into the “traditional” vs. oral arms of the study. Outside of the amount of preoperative, intraoperative and postoperative fluids given to the patients, there is no difference in the treatment or outcome measures between the 2 groups.

11. Statistical calculations- please refer to section 10, methods of evaluation

12. Confidentiality of the data.

- Data will be collected on a password protected excel spreadsheet that will be stored on a Centura password protected computer.
- All data collected will be de-identified.

Data sharing.

With whom will *identifiable* (contains any of the 18 identifiers) data be shared outside the immediate research team? For all that apply, explain confidentiality measures. Include data use agreements, if any.

Data will be shared with:		Name/Description/s
	No one	
	Coordinating Center	
	Statisticians	
x	Other researchers	Douglas A. Dennis, MD; Jason M. Jennings, MD; Todd Miner, MD; Charlie C. Yang, MD, , Mauricio Mejia, MD, Roseann Johnson (research coordinator), Daniel Levy (research data entry clerk), Catherine Eschen (clinical research associate).
	Registries	
	Sponsor/s	
	External labs for additional testing	
	Journals	
	Publicly available dataset	
	Other	

Data security for storage and transmission. Include all that apply.

For electronic data stored on a desk top computer:

<input checked="" type="checkbox"/> Secure network	<input checked="" type="checkbox"/> Password access	<input type="checkbox"/> Data encryption	<input checked="" type="checkbox"/> Password protected file(s)
<input type="checkbox"/> Other comparable safeguard (describe):		<i>Data will be de-identified</i>	

For portable computing devices/external storage devices (e.g. laptop computer, PDA, CDs, memory sticks):

<input checked="" type="checkbox"/> Power-on password	<input type="checkbox"/> Data encryption
<input checked="" type="checkbox"/> Automatic log-off	<input checked="" type="checkbox"/> Password protected file(s)
<input type="checkbox"/> Other comparable safeguard (describe): <i>Data will be de-identified</i>	

For hardcopy data (including human biological specimens, CDs, tapes, etc.):

<input type="checkbox"/> Data de-identified by research team (stripped of the 18 identifiers)	<input checked="" type="checkbox"/> Locked suite or office
<input type="checkbox"/> Data coded by research team with a master list secured and kept separately	<input checked="" type="checkbox"/> Locked cabinet
<input type="checkbox"/> Other (describe): _____	

Post-study disposition of identifiable data or human biological materials.

All identifiable data will be destroyed 7 years after completion of the study.

13. References

1. Ann Surg. 2009 Feb;249(2):181-5. doi: 10.1097/SLA.0b013e31818b73dc. Impact of different crystalloid volume regimes on intestinal anastomotic stability.
2. Int J Colorectal Dis. 2010 Apr;25(4):491-8. doi: 10.1007/s00384-009-0854-4. Epub 2009 Nov 27. Colloid vs. crystalloid infusions in gastrointestinal surgery and their different impact on the healing of intestinal anastomoses.
3. Surgery. 2013 Sep;154(3):596-603. doi: 10.1016/j.surg.2013.04.010. Epub 2013 Jul 19. Intraoperative crystalloid overload leads to substantial inflammatory infiltration of intestinal anastomoses-a histomorphological analysis.

14. Other Attachments such as any study tools that you are going to be using and/or giving to study participants (e.g. patient/participant questionnaires/surveys, diaries, reminder cards, advertisements etc.)

- **Physical Therapy Log**
- **Patient Data Log**
- **Random Envelope selection**