



# **Is Joint Arthroplasty a Viable Option for Patients with Hemophilia? An Evidence Based Review**

Melanie Marshall, MSPT

DPT Spring Symposium

UCSF/SFSU Graduate Program in Physical Therapy

May 3, 2008





# INTRODUCTION

- The Problem: Jt bleeds cause potentially severe arthropathy in hemophilia pts
  - Can cause severe pn, functional limitations, disability
- Target jt: recurrent bleeding ( $\geq 4$  x in 6 mo's or 20 lifetime episodes)
- Treatment:
  - Conservative: factor infusions, PT
  - Surgical: Synovectomy, Total Joint Arthroplasty (TJA)



# Significance of the Problem

- More and more TJA procedures being performed
- Before advent of factor replacement therapy (mid-20th century) hemophilia pts lived with inevitable pn and disability
  - Surgical intervention was futile since prob would return
- Factor replacement therapy continues to improve
  - not effective enough to prevent jt bleeds completely
  - esp. in severe or inhibitor pts with hemophilia

Greater joint disease  
severity



Greater likelihood pt  
will need TJA



# Relevance to Physical Therapy

- Physical therapy is the conservative tx of choice for pts not undergoing TJA
- PT is crucial post-op to help pt regain their ROM, strength and fxn
- Need for PT intervention rises with the number of TJA's in subjects with hemophilia
- Critical for PT's to be educated
  - unique physiology of hemophilia
  - literature on hemophilia pop/TJA to make clinical decisions based on valid research



# The Primary Question



- In patients with hemophilia who experience chronic problems related to bleeding and pain in target joints, can an arthroplasty be safely performed to improve range of motion, pain relief and function?
- Foreground question
  - P=Pts with hemophilia
  - I=Joint Arthroplasty
  - C=Outcomes for arthroplasty compared to outcomes for patients treated conservatively
  - O=Decreased pn, increased function, increased ROM, adverse events



# Hypothesis

- Ho: There will be no sig. diff in ROM, pain and function between pts with hemophilia who receive a joint arthroplasty and pts with hemophilia who receive conservative tx
- Hi: There will be sig. diff in ROM and function in patients with hemophilia who receive a joint arthroplasty compared to those with hemophilia who receive conservative treatment



# Expected Findings

- TJA should be reserved for extreme cases of joint impairments when conservative tx has failed
  - Potential complications of surgery exacerbated by hemophilia



# Theoretical Construct

- Hemarthrosis: loss of function due to pain, decreased ROM and decreased strength
- Surgery is risky and can cause problems such as infection and neuropathy
  - Esp in severe and inhibitor pts with hemophilia
- Comorbidities such as HIV and HCV can exacerbate these probs
- TJA performed when pt has lost sufficient function with conservative tx that potential benefits of surgery may outweigh risks

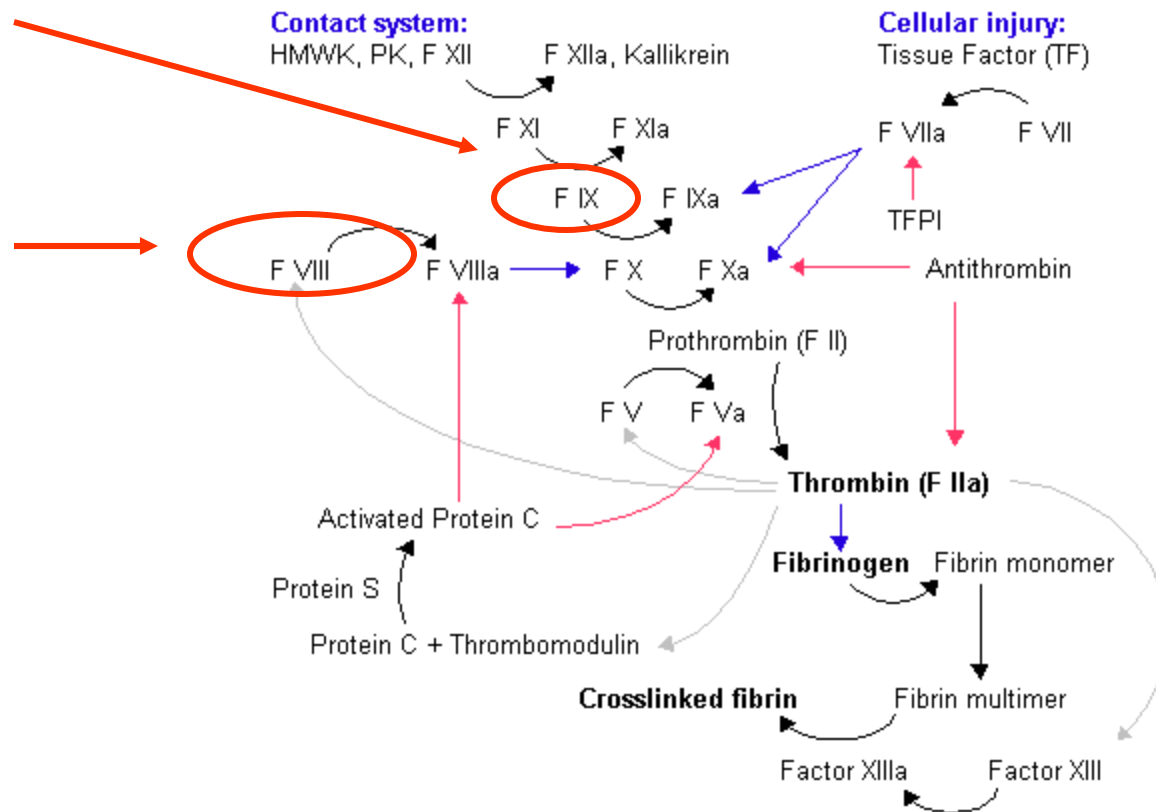


# Background: Hemophilia

- Congenital x-linked bleeding disorder
- Pt missing or have deficient blood clotting factors (proteins) that control bleeding
- As a result excessive bleeding occurs
- Males (hemizygous with XY chromosome) show effects of disease
- Females (heterozygous with XX chromosome) are carriers
- Inhibitors: patient develops antibodies to prophylactic factor replacement therapy

# Coagulation

- Hemophilia A: most common- Factor VIII deficiency
- Hemophilia B: Factor IX deficiency
- Von Willebrand's disease: von Willebrand Factor deficiency





# Incidence/Prevalence

- **Average** incidence of hemophilia A and B in six of the United States (CO, GA, LA, MA, NY, OK) reported to be 1 in 5,032 male births in 1998
- Von Willebrand's disease occurs in approximately 1.10% of the U.S population
- **In one systematic review**, prevalence of inhibitors in unselected hemophilia A populations in the UK found to be 5-7%
- Before 1985, factor replacement therapy not screened for HIV
  - From 1979 through 1998, 4,781 deaths reported among persons with hemophilia A
  - 47% HIV-related



# Target Joints

- 5 most common:
  - Knee (50.9%)
  - Ankle (42.8%),
  - Elbow (38.5%),
  - Shoulder (13.3%)
  - Hip
- Recurrent bleeding prevents jts from regaining ROM, strength and normal appearance
- Factor replacement therapy and physical therapy used as preventative tx
- Permanent changes: OA and contractures



knee bleed

# ● ● ● | TJA Complications



## ○ **Perioperative:**

- Blood loss
- Infection
- Early hemorrhage
- Wound breakdown
- Intraoperative fracture
- Anesthetic problems
- Medical complications such as cardiovascular, respiratory, renal, electrolytic

## ○ **Postoperative:**

- Neuropathies
- Fractures
- Arthofibrosis
- Aseptic loosening
- Infection



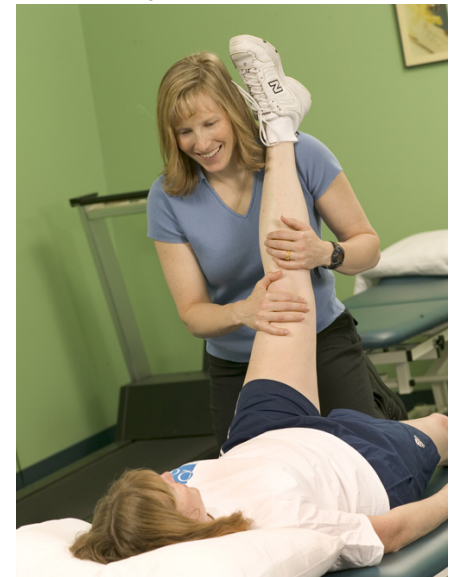
# TJA Complications

- Additional hemophilia comorbidities: obesity, HIV, HCV, other blood transfusion diseases
  - pts **immunocompromised**, delaying healing and adding to complications
- TJA in non-hemophilia population has high success rate of  $\geq 90\%$  for hip and knee replacement
- **Highly invasive** procedure
  - dislocation of the joint
  - removal of ligaments
  - drilling of the adjoining bones to place the prosthesis
  - suturing of the soft tissue and skin
- High amount of **bleeding** involved which is detrimental to hemophilia pts
  - **Multi-disciplinary approach** in peri-operative hemostasis management to ensure pt's safety
  - Higher risk of infection, hemorrhage and other complications compared to non-hemophilia patients



# Post-op PT for TJA

- **Normal post operative physical therapy for TJA involves:**
  - Early passive jt mobilization and AROM ex's
  - Progressive strengthening
  - Gait training (if LE)
  - Postural ed and scapulohumeral rhythm (if shoulder)
  - Patient education on activities to avoid, body mechanics, pn mgmt
  - Possible splinting and orthotics
  - Solidifying a home exercise program
- Ideally pt would regain functional ROM of jt
  - Ex. knee in gait is 2 to 70 degrees of flexion





# Post-op PT for Patients with Hemophilia

- Rehab similar to normal patients' PT
  - Less aggressive, esp in inhibitor and severe hemophilia pts due to bleeding precautions
- Other differences:
  - Factor infusion therapy
  - Possible increased need for pre-op PT



# Search Methods: Sources of Search

- Pub Med
- Ovid
- Cochrane
- Pedro
- Hooked on Evidence



# Search Methods: Keywords



- Arthroplasty
- Joint replacement
- Total joint arthroplasty
- Total joint replacement
- Hemophilia
- Haemophilia
- Combination of terms



# Inclusion/Exclusion Criteria

- **Level of Evidence:** I-IV
- **Type of Study:** Outcomes studies published within the last 8 years (none before 2000 and no case studies or opinion articles)
- **Subjects:** Patients with hemophilia A or B or Von Willebrand's disease with or without inhibitors
  - Elbow, knee, shoulder or hip arthroplasties
  - Surgery performed from 1970 to 2007
- **Outcomes:** At least one outcome variable needs to be reported (e.g. ROM, functional ability, pn, strength, harm)
- **Control or Comparison Group:**
  - Ideally each study will include an experimental and a control group
  - If the outcomes are reported only on one group, the study will still be included



# Data Analysis: Evidence Based Statistics

- Proportional percent change
- Mean weighted difference
- Effect size (tested for significance)
- Confidence interval
- % of patients suffering harm



# Study Findings

- Total # of studies found for primary and secondary questions: 25
- Number of studies for secondary questions: 14
- Number of studies for primary question: 11



# Types of Studies

Author/year	Type of Study	Evidence Level
1)Habermann at al 2007	Single center outcomes study	III
2)Cohen et al 2000	Single center outcomes study	III
3)Powell et al 2005	Single center outcomes study	III
4)Hicks et al 2000	Multiple centers outcomes study	IV



# Types of Studies

Author/Year	Type of Study	Evidence Level
Fehily et al 2001	Single center outcomes study	III
Norian et al 2002	Single center outcomes Study	III
Legroux-Gerot et al, 2003	Single center outcomes study	III
Kamineni et al 2004	Case Series	III



# Types of Studies

Author/Year	Type of Study	Evidence Level
Rodriguez-Merchan et al 2007	Single center outcomes study	III
Silva et al 2005	Single center outcomes study	III
Chapman-Sheath et al 2003	Single center outcomes study	III



# Results: TKA Studies

Study	# of pts	Type of Hemophilia	Follow-up Period
Rodriguez-Merchan 2007	30 pts/ 35 TKA's	Hemo A: 25 Hemo B: 5	Mean: 7.5 yrs (1-10)
Silva et al 2005	68 pts/ 90 TKA's	Hemo A: 60 Hemo B: 8	Varies by measure
Legroux-Gérot et al 2003	12 pts/ 17 TKAs	Hemo A: 9 Hemo B: 3	Mean: 54 mo's (8-132)
Fehily et al 2002	8 patients/ 9 TKA's	Hemo A: 5 Hemo B: 4	Mean: 51 mo's (6-103.2)
Cohen et al 2000	16 pts/ 21 TKA's	Hemo A: 16	Mean: 5.6 years (2-10)



# Results: TKA ROM

Study	ROM: Pre-op→Post-op
Rodriguez-Merchan 2007	Flexion arc: <b>Mean 60→75</b> Flexion contracture: <b>Mean 20→10</b>
Silva et al 2005	Flexion arc: <b>Mean 59→75</b> Flexion contracture: <b>Mean 18→8</b>
Legroux-Gérot et al 2003	Flexion arc: <b>Mean 66→Mean 89</b>
Fehily et al 2002	No ROM measurements taken
Cohen et al 2000	Flexion arc: <b>Mean 72.4→83.4</b> Extension lag: reduced in milder range only



# Results: TKA Pain

Study	Pain: Pre-op→Post-op
Rodriguez-Merchan 2007	No pain measurements taken
Silva et al 2005	Post-op measurements only: <b>Mild or occasional pn reported</b>
Legroux-Gérot et al 2003	Post-op measurements only: <b>10 pts no pn, 2 pts residual pn</b>
Fehily et al 2002	<b>6.9→0</b> (American Knee Society scoring)
Cohen et al 2000	<b>8 moderate, 6 severe→1 moderate, 6 mild, 7 no pain</b>



# Results: TKA Function

Study	Function: Pre-op→Post-op
Rodriguez-Merchan 2007	Knee society score: <b>excellent in 27 knees (77%), good in 6 (17%) knees, fair in 2 knees (6%)</b>
Silva et al 2005	Knee society score: <b>Mean 88.7 points</b>
Legroux-Gérot et al 2003	Cleveland Knee rating: <b>Mean score increased 19 points</b>
Fehily et al 2002	Am Knee Society score: <b>all &gt;90/100</b>
Cohen et al 2000	H.S.S. Score: Knee score: <b>24.1 (poor)→77.5 (good to excellent)</b> Functional score: <b>mean 23.2 →84.4</b>



# Results: TKA Complications

Study	Complications
Rodriguez-Merchan 2007	1 knee: <b>removal of component (staph infection)</b> 4 yrs post-op <b>Acute hemarthrosis</b> occurred in 1 pt with an inhibitor
Silva et al 2005	<b>Acute hemarthrosis</b> in 7 knees <b>Heterotopic ossification</b> in 2 knees Coombs-positive <b>hemolysis</b> in 3 pts 1 <b>wound dehiscence</b> at time of knee manipulation 1 nonfatal <b>pulmonary embolism, infection</b> in 14 knees
Legroux-Gérot et al 2003	5 pts with <b>hemarthrosis</b> 1 pt <b>skin necrosis</b> 4 <b>revisions</b> immediately post-op, 1 revision 4 yrs post-op 1 <b>jaundice</b> 1 <b>RSD</b>
Fehily et al 2002	1 <b>PUO</b> (pyrexia of unknown origin) 1 <b>intra-articular bleed</b> 2 days post-op
Cohen et al 2000	1 <b>prosthesis removal</b> (inhibitor pt) 1 superficial <b>infection</b> , 4 pts <b>febrile</b> (no clear infection) 1 <b>patellar dislocation</b> , 2 manipulations due to <b>fiboarthrosis</b>



# Results: THA Study

Study	# of pts	Type of hemophilia	Follow-up Period
Habermann et al 2007	13 pts, 15 THA's	Hemo A: 10 pts VWD: 3 pts	Mean: 132 mo's (12-363)



# Results: THA Study

Measure	Results (Habermann et al)
ROM (mean of sum of 3 standard directions)	<b>90 deg pre-op → 189.6 deg post-op</b>
Pain (Subjective improvement)	<b>Mean 2.0 → 5.4 points</b>
Function (Harris Hip score)	<b>Mean 48 (32-66) → 89 (76-100)</b>
Complications	Post-op: 1 <b>septic loosening</b> (HIV pt), 1 <b>candida infection</b> (HIV pt) – both deceased



# Results: TEA Studies

Study	# of pts	Type of hemophilia	Follow-up Period
Kamineni et al 2004	5 pts/8 TEA's	Hemo A: 3 (1 inhibitor) Hemo A + B:1 VWD: 1	Mean 121.8 mo's (84-153)
Chapman-Sheath et al 2003	5 pts/ 7 TEAs	All Hemo A	Mean 42 mo's (25-65)



# Results: TEA Studies

Measure	Results
Flexion arc ROM	Kamineni: <b>Mean 38 pre-op → 89 post-op</b> Chapman-Sheath: <b>Mean 50 pre-op → 93.5 post-op</b>
Pain	Kamineni: <b>4/45 pre-op → 41/45 post-op</b> Chapman-Sheath: <b>severe pain pre-op → no pain in 4 elbows and 2 mild pn</b>
Function	Kamineni: <b>24/100 pre-op → 90/100 post-op (Mayo Elbow Performance)</b> Chapman-Sheath: no measurement
Complications	Kamineni: 1 <b>prosthesis removal</b> , 1 <b>infection</b> , 1 <b>chronic pain</b> Chapman-Sheath: 1 <b>ulnar nn palsy</b> , 1 <b>axillary vein thrombosis</b> , 1 <b>revision</b>



# Results: Harm Studies

Study	# of pts	Type of hemophilia	Follow-up Period
Norian et al 2002	38 patients/ 53 TKA's	Hemo A: 33 Hemo B: 5	Mean 110 mo's (24-246)
Hicks et al 2001	73 pts/102 TJA's (74 TKA's, 27 THA's, 1 TEA	Hemo A: 67 Hemo B: 2 Not stated: 4	Mean 5.7 yrs (0.1-20.8)
Powell et al 2005	32 pts/ 51 TJA's (35 TKA's and 16 THA's), 19 AIDS pts	Hemo A: 29 Hemo B: 2 Factor VII deficiency: 1	Mean 80 mo's (2-323)



# Results: Harm Studies

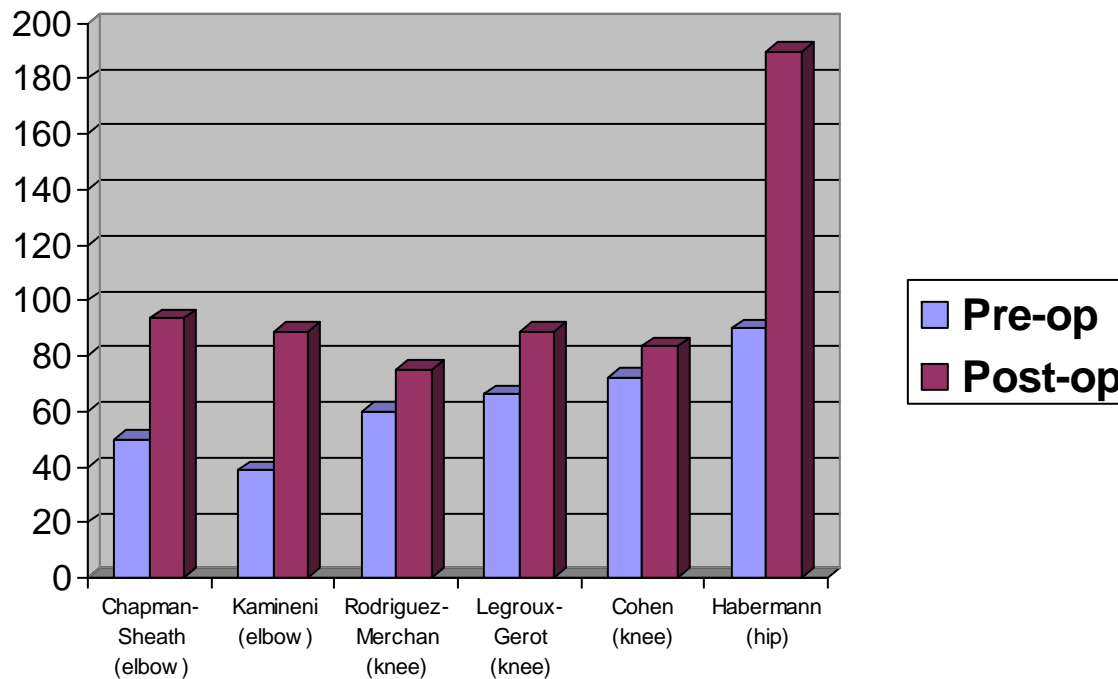
Study	Results
Norian et al 2002	<ul style="list-style-type: none"><li>○29 pts HIV+ (76%)</li><li>○10 revisions, 6 infections, 5 mechanical failures</li><li>○Survival rate: 90% after 5 yrs</li></ul>
Hicks et al 2001	<ul style="list-style-type: none"><li>○All pts HIV+</li><li>○21 pts had deep sepsis (17 from primary -<b>18.7%</b>, 4 from revision- <b>36.3%</b>) – <b>44% resolved</b></li><li>○Survival Rate: 55% 10 yrs post-op for those already diagnosed w/HIV</li><li>-sepsis free grp: 71.8% survival rate 10 yrs post-op</li></ul>
Powell et al 2005	<ul style="list-style-type: none"><li>○3 revisions, 6 infections</li><li>○59% Mortality (32 pts)</li><li>-82% of deaths HIV-related</li><li>-No deaths resulted from joint infection</li></ul>



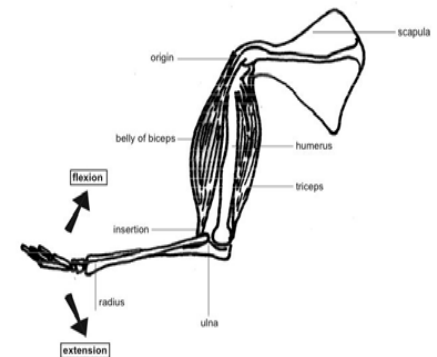
# Results: HIV and TJA

- Conclusion from Powell et al:
  - HIV not a contraindication to TKA or THA for patients with hemophilia
- Silva et al:
  - Infection occurred in 16%: 14 knees/10 pts total
    - 4/30 HIV- pts (13%)
    - 10/60 HIV+ pts (17%)
    - Similar overall prevalence in HIV+ versus HIV- patients

# Flexion Arc ROM

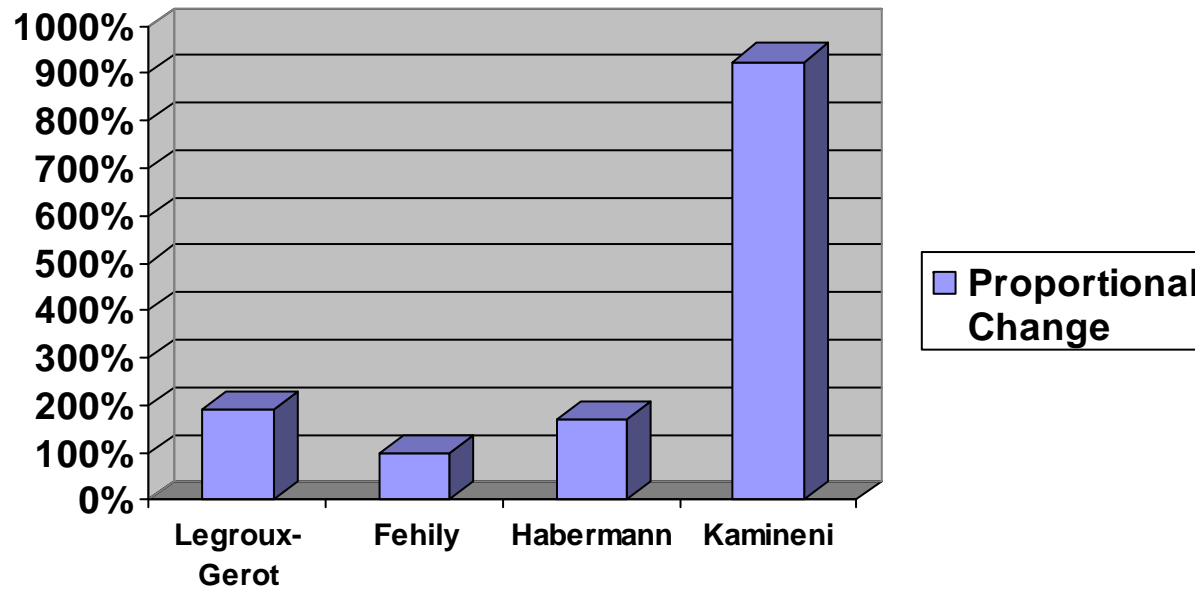


- Mean Weighted % Change: 0.653 (65.3%)
- Standard Deviation of Mean Weighted Difference: 0.025
- SEM= 0.00158
- Effect Size=6.1
- CI= +/- 1.96 (SEM): -0.00310 to 0.00310





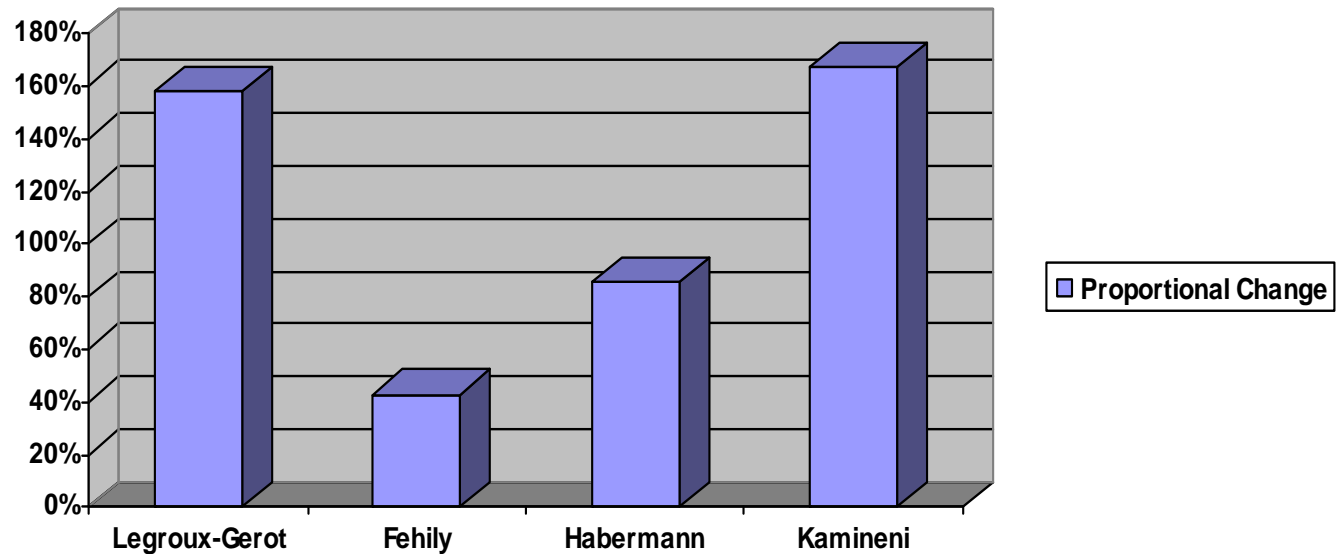
# % Change Pain



- Mean Weighted Proportional Change:  $2.504 = 250.4\%$
- Standard Deviation of Mean Weighted Difference: 0.217
- SEM: 0.106
- **Effect Size=11.5**
- CI=  $\pm 1.96(\text{SEM}) = -0.208$  to  $0.208$



# % Change Function



- Mean Weighted % Change: 1.28  
Standard Deviation of Mean Weighted Difference: 0.305
- SEM: 0.0126
- Effect Size=4.20
- CI= +/- 1.96(SEM)= -0.0247 to 0.0247



# Adverse Events

<b>Infections</b>	<b>52 patients total</b>
<b>Hemarthrosis</b>	<b>7 patients total</b>
<b>Revisions</b>	<b>10 patients total</b>
<b>Manipulations</b>	<b>2 patients total</b>
<b>Loosening</b>	<b>3 patients total</b>
<b>Persistent Severe Pain</b>	<b>1 patient</b>
<b>Anticoagulants in blood</b>	<b>2 patients total</b>



# Harm Outcomes

## Percentage of Patients Suffering Harm Post Arthroplasty:

<u>Study</u>	<u>Number of Subjects</u>	<u>% Resulting in Harm</u>
Silva:	90	16%
Legroux-Gerot:	17	47%
Habermann:	15	13%
Cohen:	21	24%
Kamineni:	8	38%
Rodriguez-Merchan:	35	6%
Chapman-Sheath:	7	14%
Fehily:	9	0%
Powell:	51	10%
Hicks:	102	21%
Norian:	53	19%



*Total harm in all studies*  
*(408 TJA's)= **19%***



# Null Hypothesis

- There will be no sig. difference in ROM, pain and function between patients with hemophilia who receive a joint arthroplasty and patients with hemophilia who receive conservative treatment
  - No studies were compared to a control grp with conservative tx (outcome studies only)
  - Outcomes in all studies showed **large positive changes** in pre-op vs post-op ROM, pain and function
  - Can reject null using low but consistent levels of evidence



# Discussion: Limitations of Search

- Only outcomes studies were available (level III-IV)
  - RCT's, systematic reviews or meta-analyses would provide stronger evidence
- Studies used different values for pn, ROM and function
  - Some did not have pre-op versus post-op measurements
- Effect size calculations not completely accurate as do not have all of the values to calculate SD
  - Partially accounted for by calculating MWD
- No comparisons made between TJA and conservative tx such as PT
- As all studies were retrospective, none of them utilized blinding – Bias?
- TEA has a higher complication rate than TKA or THA



# Future Research

- Research needed to compare TJA (experimental grp) to conservative tx (control grp)
- Need Level I and II studies
- Difficult to randomize as surgery is invasive
  - Could create 2 grps in which all pts eventually would have TJA, and only some would receive pre-op PT
  - Ethical considerations?
- Evaluate the benefit of physical therapy pre- and post-surgery



# Recommendations for PT Practice

- PTs must be aware of best protocols for treating pts with hemophilia
- History:
  - frequency of bleeds
  - target joints
  - method of factor replacement
  - presence of inhibitors
  - Level of activity (recreational and occupational)
- Observation:
  - bruises, hematomas
  - contractures (joint position)
  - Swelling, tissue bulk and joint use
- Neurological status: N/T?



# Recommendations for PT Practice

- Acute Stage:
  - RICE
  - Splinting
  - patient ed
- Subacute Stage:
  - gradual increase of activity/exercise
  - proprioceptive/balance activities
  - Modalities
  - gentle stretching with muscle bleeds
  - continued patient and family education
- Chronic: same as subacute with increased vigor



# Recommendations for PT Practice

- PTs must stay current on reported outcomes of TJA in pts with hemophilia
- Pts should receive conservative tx (PT) first due to risks
- Tell pts it is a good option if they are:
  - severely limited in fxn
  - have significantly decreased jt ROM
  - suffer severe pn
  - conservative tx fails
- Let them know that the research suggests that overall benefits of TJA outweigh risks if fxn is severely limited



# Conclusions

- TJA is not widely studied in the hemophilia pt population
- These outcomes studies show it is a viable option for severe hemophilia pts
  - Improvements in pn, ROM and fxn
  - Mild increase in adverse outcomes compared to non-hemophilia pts due to comorbidities associated w/hemophilia
  - HIV does not significantly increase percentage of adverse outcomes in TJA
  - More research needed to compare to conservative tx
    - Randomized, blinded
    - Meta-analyses, systematic reviews



# Thank you!

## Questions? Comments?

- Special Thanks to:
  - Pattye Tobase, DPT, PT
  - Nancy Byl, PhD, PT, FAPTA
  - Patrick Fogarty, MD
  - Susan Karp, RN