To Use or Not to Use Liposomal Bupivacaine: Managing Pharmacotherapy Costs in Orthopedic Procedure Pain Management

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Disclosure

• Dr. Heather Weese - Nothing to disclose
• Dr. Yin Wong – Employee of Wolters Kluwer Health: a medical content company
Today’s Presentation Format

1. Literature Review of liposomal bupivacaine (LB) use in orthopedic procedures: total knee arthroplasty and total hip arthroplasty
2. Health economic outcomes study of liposomal bupivacaine use at Community Health Systems
3. Formulary management approach for liposomal bupivacaine
Learning Objectives

• Discuss the current literature on the efficacy and safety of liposomal bupivacaine in orthopedic procedures

• Describe the findings of an enterprise-wide liposomal bupivacaine health economic study

• Propose new strategies on managing liposomal bupivacaine use for possible cost savings
Liposomal Bupivacaine Literature Review

Use of Liposomal Bupivacaine in Orthopedic Procedures (TKA/THA)
Background

Liposomal Bupivacaine Injectable Suspension (Exparel®)

• Liposomal bupivacaine (Exparel®) approved by FDA in Nov. 2011 indicated for administration into the surgical site to produce postsurgical analgesia
  — Bone model – Bunionectomy
  — Soft tissue model – Hemorrhoidectomy

• Comparing Exparel® to bupivacaine hydrochloride:
  — Differ in duration of action: 24 – 96 hours vs. 2 – 9 hours, respectively
  — Half life: 24 – 34 hours vs. 2.1 hours, respectively

• Efficacy demonstrated in trials: decrease in pain intensity score and reduction in opioid consumption

Picture credit: Which Drug is Better for Post-op Pain Control?
https://www.outpatientsurgery.net/surgical-services/pain-management/which-drug-is-better-for-post-op-pain-control–ambulatory-anesthesia-15
Background

Food and Drug Administration Warning

- September 2014 – FDA issued a warning letter to Pacira Pharmaceuticals, Inc. for Exparel® (liposomal bupivacaine):
  - Administration: Inadequate directions for use
  - Indications: Claims suggest Exparel® can be used for other procedures but evidence for Exparel® efficacy and safety came from bunionectomy and hemorrhoidectomy
  - Overstatement of efficacy: claims suggest Exparel® effectiveness last up to 72 hours but evidence suggest that Exparel® effectiveness beyond
  - 24 hours has not been demonstration type or site
Background, continued

Food and Drug Administration Warning

• March 2016 – Resolution of FDA Legal Action:
  — Administration: Exparel® can be mixed with bupivacaine HCl
  — Indications: use of Exparel® for administration at surgical site is NOT limited to any specific surgery type or site
  — Efficacy: significant treatment effect for Exparel® compared to placebo for the first 72 hours in the pivotal hemorrhoidectomy study
Literature Review

Methods

Electronic databases searched: CENTRAL (Cochrane Library), MEDLINE (Ovid), EMBASE (Ovid), International Pharmaceutical Abstracts (Ovid), SCOPUS

Medical subject headings (MeSH) or equivalent and key terms used: liposomal bupivacaine, Exparel, postoperative pain, postoperative complications, orthopedic, knee arthroplasty or replacement, hip arthroplasty or replacement

Criteria for Literature Review

<table>
<thead>
<tr>
<th>Types of studies</th>
<th>Types of outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomized controlled trials</td>
<td>• Pain scores</td>
</tr>
<tr>
<td>• Pro/retrospective evaluative studies</td>
<td>• Opioid consumption</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of participants</th>
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<tbody>
<tr>
<td>• Age ≥ 18 undergoing total knee or hip arthroplasty receiving liposomal bupivacaine</td>
<td>• Adverse events</td>
</tr>
<tr>
<td></td>
<td>• Range of motion/ambulation distance</td>
</tr>
<tr>
<td></td>
<td>• Length of stay/satisfaction</td>
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</tbody>
</table>

Results

• Total of 115 articles from 5 databases identified
• Investigator screened the results and removed abstracts/articles based on prespecified criteria
  — 5 randomized controlled trials
  — 10 cohort/case-control studies
RANDOMIZED CONTROLLED TRIALS ANALYSIS
## Literature Review
### Summary Table of Analyzed Randomized Controlled Trials

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</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>138</td>
<td>111</td>
<td>80</td>
<td>70</td>
<td>105</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Adults, TKA</td>
<td>Adults, TKA</td>
<td>Adults, TKA</td>
<td>Adults, TKA</td>
<td>Adults, TKA</td>
</tr>
<tr>
<td>Study Location</td>
<td>Multicenter; US and Czech Republic</td>
<td>Single center; US</td>
<td>Single center; US</td>
<td>Single center; US</td>
<td>Single center; US</td>
</tr>
<tr>
<td>Study Design</td>
<td>Phase 2, RCT, DB, PG, dose-ranging</td>
<td>PRO, Blinded, RCT</td>
<td>RCT</td>
<td>PRO, DB, RCT</td>
<td>PRO, RCT</td>
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<tr>
<td>Follow-up</td>
<td>36 Days</td>
<td>4 days</td>
<td>4 days</td>
<td>10 days</td>
<td>42 days</td>
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<tr>
<td>Intervention</td>
<td>PAI LB vs. Bupivacaine + Epi</td>
<td>PAI LB vs. Femoral nerve block</td>
<td>PAI LB vs. combo cocktail¥</td>
<td>PAI LB vs. Modified Ranawat suspension*</td>
<td></td>
</tr>
<tr>
<td>Primary endpoints</td>
<td>AUC for NRS-A through Day 4</td>
<td>Pain scores (VAS)</td>
<td>Pain score (NRS)</td>
<td>Pain scores (NRS)</td>
<td>Pain scores (VAS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>post-op opioid consumption</td>
<td>post-op opioid consumption</td>
<td>post-op opioid consumption</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>NRS-A and NRS-R</td>
<td>Range of motion (ROM)</td>
<td>Adverse events</td>
<td>post-op opioid consumption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC of NRS-R through Day 4</td>
<td>Adverse events</td>
<td>Time to resumption of normal activities</td>
<td>ambulation distance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adverse events</td>
<td>Length of stay</td>
<td></td>
</tr>
</tbody>
</table>

TKA = total knee arthroplasty; RCT = randomized, controlled trial; DB = double blinded; PG = parallel-group; PRO = prospective; PAI = periarticular injection; LB = liposomal bupivacaine; AUC = area under the curve; NRS = numeric rating scale; NRS-A = numeric rating scale on activity; NRS-R = numeric rating scale at rest; VAS = visual analog scale.

¥ combo cocktail consists of: ketorolac 30mg, morphine PF 5mg, epinephrine 0.6mg, Ropivacaine 400mg, QS to 100mL with 0.9% Normal Saline

*Ranawat cocktail consists of: 49.25mL of Ropivacaine (5mg/mL), 0.5mL of epinephrine (1mg/mL), 1mL of ketorolac (30mg/mL), 0.8mL of clonidine (0.1mg/mL), diluted with 48.45mL of 0.9% Normal Saline
Comparison of Overall Pain Scores

Forrest Plot

<table>
<thead>
<tr>
<th>Studies</th>
<th>Mean Overall Pain Score Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bramlett 2012</td>
<td>-0.900 (-3.378, 1.578)</td>
</tr>
<tr>
<td>Schroer 2015</td>
<td>-0.300 (-1.069, 0.469)</td>
</tr>
<tr>
<td>Surdam 2015</td>
<td>0.500 (-0.808, 1.808)</td>
</tr>
<tr>
<td>Snyder 2016</td>
<td>-0.790 (-1.618, 0.038)</td>
</tr>
<tr>
<td>Collis 2016</td>
<td>2.370 (1.987, 2.753)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0.259 (-1.397, 1.916)</td>
</tr>
</tbody>
</table>

*SOC = Standard of Care: PAI bupivacaine ± epinephrine, femoral nerve block, concentrated cocktail, Ranawat suspension

% Weight:
Comparison of Postoperative Opioid Consumption

Forrest Plot

Favors Liposomal Bupivacaine  Favors SOC

<table>
<thead>
<tr>
<th>Studies</th>
<th>Postop Opioid Consumption Mean Difference</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroer 2015</td>
<td>-2.400 (-14.475, 9.675)</td>
<td>6.09</td>
</tr>
<tr>
<td>Surdam 2015</td>
<td>1.233 (-3.117, 5.583)</td>
<td>29.97</td>
</tr>
<tr>
<td>Snyder 2016</td>
<td>-4.310 (-8.369, -0.251)</td>
<td>32.42</td>
</tr>
<tr>
<td>Collis 2016</td>
<td>1.180 (-2.983, 5.343)</td>
<td>31.52</td>
</tr>
<tr>
<td>Overall (I^2=35.46 %, P=0.199)</td>
<td>-0.802 (-3.916, 2.311)</td>
<td></td>
</tr>
</tbody>
</table>

*SOC = Standard of Care: PAI bupivacaine ± epinephrine, femoral nerve block, concentrated cocktail, Ranawat suspension
Other Outcomes & Considerations

Other Outcomes

• Range of motion (ROM)
  — Surdam et al. 2015: greater ROM for FNB grp but only the first 24 hrs
  — Collis et al. 2016: no difference

• Ambulation distance
  — Surdam et al. 2015: no difference but more LB patients can ambulate on POD#0
  — Collis et al. 2016: LB grp had increase ambulation distance trend but no statistical significance

• Adverse events
  — Bramlett et al. 2012: no difference
  — Surdam et al. 2015: no difference
  — Snyder et al. 2016: 67.9% in control grp reported nausea vs. 32.1% in LB grp (p<0.05)

• Length of stay (LOS)
  — Surdam et al. 2015: avg. LOS is lowered in the LB grp (2.36 ± 0.71) vs. FNB grp (2.65 ± 0.48), (p=0.03) \( \rightarrow \) mean difference = 6.9 hours

Considerations

• Post-op opioid consumption
  — Bramlett et al. 2012: no statistical significance to that endpoint, time to resumption of normal activities

• Interventions
  — PAI LB vs. (1) Bupivacaine +/- Epi
    (2) Femoral Nerve Block
    (3) Combo cocktail
  — Surdam et al. 2015: while FNB improves pain control and flexion on POD#0, FNB contributes to quadriceps weakness, delaying ambulation.
    ▪ LB group had a 6x increase in the number of patients who can ambulate the day of surgery

• Variation between study site specific pain management protocol
## Study Site Based Multimodal Pain Control Protocol

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<tbody>
<tr>
<td>Study Site</td>
<td>Multicenter</td>
<td>Single center, single surgeon</td>
<td>Single center, single surgeon</td>
<td>Single center</td>
<td>Singled center, single surgeon</td>
</tr>
<tr>
<td>Pre-op education</td>
<td>1 hour total knee education</td>
<td>education class</td>
<td>education class</td>
<td>education class</td>
<td>education class</td>
</tr>
<tr>
<td>Before surgery</td>
<td>APAP 1000mg TID x 24 hrs</td>
<td>APAP per instruction x 72 hrs</td>
<td></td>
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<tr>
<td>Pre-op meds</td>
<td>IV Fentanyl or analogs allowed</td>
<td>Celecoxib 400mg x 1</td>
<td>Ondansetron</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>OxyCONTIN 20mg x 1</td>
<td>Oxycodone SR</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Scopolamine patch 6mg x 1</td>
<td>Scopolamine patch (if &lt;65)</td>
<td></td>
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<tr>
<td>Intra-op meds</td>
<td>Spinal fentanyl 25mcg + bupivacaine 15mg</td>
<td>Spinal bupivacaine 0.75%</td>
<td>Spinal regional anesthesia ropivacaine 0.75%</td>
<td>general anesthesia propofol 1%</td>
<td>single shot femoral &amp; sciatic block with ropivacaine</td>
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<tr>
<td></td>
<td>Dexamethasone 8 mg</td>
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<tr>
<td></td>
<td>Ondansetron 8mg</td>
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<tr>
<td></td>
<td>Tranexamic acid 10mg/kg (max 1000mg)</td>
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<tr>
<td>Post-op meds</td>
<td>Ketorolac 30mg IV, Ketoprofen 100mg or diclofenac 75mg x 1</td>
<td>Morphine PCA PRN</td>
<td>Ondansetron 8mg q6hrs x 24hrs then PRN</td>
<td>Ondansetron IV PRN or metoclopramide PO PRN</td>
<td>PCA</td>
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<tr>
<td></td>
<td>Rescue morphine via PCA on PRN; no basal rate</td>
<td></td>
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<tr>
<td>If PO is allowed</td>
<td>APAP 1000mg for 96 hrs</td>
<td>Celecoxib 400mg daily</td>
<td>Celecoxib BID</td>
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<tr>
<td></td>
<td>Oxycodone IR 5-10mg PO q4-6hrs PRN</td>
<td>OxyCONTIN 10mg q12hrs x 2 doses</td>
<td>Oxycodone SR q12 hrs x 2 doses</td>
<td></td>
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<tr>
<td></td>
<td>Hydrocodone or Oxycodone PRN</td>
<td>Hydrocodone q4hrs scheduled</td>
<td>Hydrocodone q4hrs scheduled</td>
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<td></td>
<td>Oxycodone PRN</td>
<td></td>
<td>Oxycodone PRN</td>
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Questions remain...

As a summary of all the RCTs on Exparel® use in TKA

1. Can the use of Exparel® lead to better postoperative pain control in orthopedic surgery?
2. Does the use of Exparel® as part of multimodal pain management protocol leads to reduction of opioid consumption? Reduction in opioid related adverse events?
3. Does the use of Exparel® associate with early ambulation and lead to shorter length of stay?
OBSERVATIONAL STUDIES ANALYSIS
Observation Studies For Exparel® (Liposomal Bupivacaine) in Total Hip/Knee Arthroplasty (THA/TKA)

Total # of Observation Studies

- 10% THA (LB vs. SOC)
- 10% TKA (LB vs. FNB)
- 20% THA/TKA
- 30% TKA (LB vs. SOC)
- 30% TKA (LB vs. Epidural)

Total of 10 observational studies from literature search

Periarticular injection of liposomal bupivacaine vs.
- Standard of Care
- Femoral Nerve Block
- Epidural

Assessed in:
- Total Hip Arthroplasty
- Total Knee Arthroplasty
## Exparel® Use in Total Hip Arthroplasty

### Periarticular Injection of Liposomal Bupivacaine vs. Standard of Care

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Barrington, et al. (2015) | Quasi-experimental study for TKA/THA (n=2248) | Pre-group: PAI bupi + morphine ± ketorolac vs. Post-group: PAI LB | - **Avg. VAS score:** 2.30 vs. 1.67 (p<0.0001)
- **% of VAS pain score as 0:** 43.4% vs. 57.3% (p<0.0001)
- **Total direct hospital costs:** avg. reduction of $1246/pt
- **LOS:** reduced from 2.69 to 2.40 days (p<0.001)

_Funded by Pacira Pharmaceuticals, did not report opioids consumption, some patients received FNB (did not specify), did not report multimodal analgesia protocol_

| Domb et al. (2014)          | Retrospective cohort study for THA (n=58) | PAI LB + bupi + epi vs. PAI bupi + epi               | - **Post-op opioid consumption:** 24mg vs. 53.35mg (p<0.0001) only in the first 24hrs; no diff after
- **VAS pain score:** no diff
- **LOS:** 1.93 days vs. 2.47 days (p≤0.05)

_No difference in pain score, reduction of opioid consumption only for first 24 hours_

| Yu et al. (2016)          | Quasi-experimental study for THA (n=1272) | Pre-group: SOC (no PAI LB) vs. Post-group: PAI LB | - **Pain scores:** LB grp less pain in the first 8 hrs (p=0.031)
- **Post-op opioid consumption:** LB grp used less narcotics for POD 0 and POD 1 (p<0.001), no diff after
- **LOS:** 2.93 vs. 2.62 days (p<0.001) mean diff = 0.31 days
- **Discharge location:** LB grp 5.19% more pts discharged home rather than rehab

_Similar pain scores except for the first 8 hours_

TKA = total knee arthroplasty; THA = total hip arthroplasty; PAI = periarticular injection; LB = liposomal bupivacaine; Bupi = bupivacaine HCl; Avg. = average; VAS = visual analog scale; LOS = length of stay; FNB = femoral nerve block; epi = epinephrine; diff = difference; SOC = standard of care; grp = group
Exparel® Use in Total Knee Arthroplasty
Periarticular Injection of Liposomal Bupivacaine vs. Femoral Nerve Block

**Liposomal Bupivacaine**
*Broome et al. (2014):* *stats significance not provided*
- Pain scores: POD#1 4.0 vs. 4.9; POD#2 4.7 vs. 5.3
- LOS: 53 vs. 60 hours
- Cost savings: $600 per patient for PAI LB

*Horn et al. (2015):*
- Physical therapy sessions: 2.3 vs. 3.5 sessions (p=0.002)
- LOS: 1.5 vs. 1.9 days (p=0.032) → avg. reduction of 0.375 days
- Cost savings: PT $480, LOS $795

*Cien et al. (2015):*
- LOS: 1.58 vs. 2.05 days (p<0.001)
- Avg. hospitalization costs: $26,472 vs. $28,546 (p<0.001)

**Femoral Nerve Block**
*Broome et al. (2014):*
- IV rescue opioid use: reduced by 19% in LB grp (not stats significant)

*Cien et al. (2015):*
- Opioid consumption: 121 vs. 199mg (p=0.075)
*Patients who received FNB also got PCA Hydromorphone post-op as part of protocol*

Favors LB  Favors FNB
**Exparel® Use in Total Knee Arthroplasty**

Periarticular Injection of Liposomal Bupivacaine vs. Standard of Care

**Liposomal Bupivacaine**

*Webb et al. (2015) No PAI*

- Opioids consumption at 48 – 72 hours: 60.97 mg vs. 89.74mg (p=0.009)
- LOS: 2.64 days vs. 3.06 days (p=0.004) in subset of patients with BMI <40, CCI 0 – 3

*Heim et al. (2015) Epidural and PAI ropivacaine + ketorolac + epi*

- Pain scores sum after POD#1: 2.0 ± 3.6 vs. 32.7 ± 23.4 (p<0.001)
- Overall opioid consumption: 18.7 ± 23.6mg vs. 42.4 ± 25.2mg (p=0.001)
- Ambulation distance POD#1: 133.8 ± 47.2 feet vs. 75.0 ± 46.7 feet (p<0.001)
- LOS: 1.04 vs. 2.0 days (p<0.001)

**Standard of Care**

*Bagsby et al. (2014) PAI ropivacaine + morphine + epi*

- Pain scores: after the first 24 hours 4.89 ± 1.35 vs. 4.38 ± 1.60 (p=0.04)
- % of patients reporting mild pain: 16.9% vs. 47.6% (no stats significance provided)
- Opioid consumption: no difference

*White et al. (2015) No PAI*

- AUC of NRS pain score: 199.6 ± 67.1mg vs. 192.9 ± 70.4mg (p=0.658)
- Opioid consumption: LB grp consumed more opioids in the first 48 hrs by 10mg (no stats significance)

Favors LB  Favors SOC
Where does Exparel® stand in terms of its use in total knee/hip arthroplasty?
Do we now have answers for the questions?
As a summary of all the observational studies + RCTs on Exparel® use in TKA/THA

1. Can the use of Exparel® lead to better postoperative pain control in orthopedic surgery?
2. Does the use of Exparel® as part of multimodal pain management protocol lead to reduction of opioid consumption? Reduction in opioid related adverse events?
3. Does the use of Exparel® associate with early ambulation and lead to shorter length of stay?
References

Health Economic Outcomes Evaluation of Liposomal Bupivacaine (Exparel®) for Orthopedic Procedures Diagnosis Related Group 469 & 470

A Community Health Systems Enterprise-wide Study
Acknowledgement

This health system study has been a collaborative effort; we would like to acknowledge the following individuals:

**Primary Investigators:**
- Heather Weese, PharmD, BCPS (CHS Pharmacy Operations & Informatics Director)
- Yin Wong, PharmD, BCPS (Health Information & Clinical Outcomes Fellow)

**Research Supervising Investigators:**
- Trent Beach, PharmD, MBA, MHA, BCPS, FASHP, FACHE (CHS Clinical Pharmacy & Education Director)
- Robert Fink, PharmD, MBA, FACHE, FASHP, BCNSP, BCPS (Quorum Health Corporation VP of Pharmacy & Ancillary Services)
- Beverly Bowman, RN, MNSc (CHS Surgical Services Senior Director)
- Kimberly Wellborn, PT, MBA (CHS Physical Therapy Services Senior Director)

We have also received assistance from the following individuals:
- Andrew Moseley Jr, CPA (CHS Clinical Analysis Director)
- Philip Odom (CHS Data Analytics & Reporting Analyst II)
- Bobby Parker, RPh (InPharmics® Founder)
- Paul Talley, MBA (CHS Quality, Risk & Management Director)
- Facility Joint Care Coordinators who participated in data collection
### Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Multicenter retrospective-prospective observational case-control study</th>
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</thead>
</table>
| **Primary Endpoint** | • Drug-cost per case (by DRGs)  
• Length of stay (LOS) |
| **Secondary Endpoints** | • Total analgesic consumption: opioid, NSAID, Ofirmev®, acetaminophen PO/PR  
• Pain intensity score  
• Ambulation distance |
| **Inclusion** | • ≥18 years of age  
• Undergoing a major joint replacement or reattachment of lower extremity surgical procedure (DRG 469/470) |
| **Exclusion** | • Pregnant or nursing  
• Concurrent surgery required analgesic treatment  
• Hypersensitivity or contraindication to bupivacaine |
| **Study Period** | • Primary endpoints: July 1<sup>st</sup> to October 31<sup>st</sup>, 2014  
• Secondary endpoints: October 1<sup>st</sup> to 31<sup>st</sup>, 2014 |
Methods: Study Timeline & Data Collection

Retrospective

Prospective

Facility-based Joint Care Coordinators

- Pain Intensity Score
- Ambulation Distance

InPharmics Tool
Query patients who meet study criteria: cases identified by DRG 469 or 470 with Exparel® use, controls identified by DRG 469 or 470.

Drug Acquisition Costs
Patients’ Length of Stay

Drug Acquisition Costs
Patients’ Length of Stay

Total Analgesic Consumption During Hospitalization

Study Period
July – September 2014

–

October 2014
Methods: Flow Chart of Enrollment

Total sample size = 2,465
- Control = 1,178
- Cases = 1,287
Results: DRG-based Drug Cost Per Case Composite Endpoint (DRG 469 + 470)

Pooled Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRG 470£ + 469¥</td>
<td>$499.41 (n=1287)</td>
<td>$205.26 (n=1178)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

£DRG 470 = Major Joint Replacement or Reattachment of Lower Extremity without Major Complications and/or Comorbidities

¥DRG 469 = Major Joint Replacement or Reattachment of Lower Extremity with Major Complications and/or Comorbidities

The 95% CI for composite primary endpoint is very similar to the DRG 470-based drug costs per case
## Results: DRG-based Drug Cost Per Case

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRG 470£</td>
<td>$497.15 (n=1264)</td>
<td>$198.54 (n=1163)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DRG 469¥</td>
<td>$1041 (n=23)</td>
<td>$979.07 (n=15)</td>
<td>Insufficient sample size for statistical analysis</td>
</tr>
</tbody>
</table>

£DRG 470 = Major Joint Replacement or Reattachment of Lower Extremity Without Major Complication and/or Comorbidity

¥DRG 469 = Major Joint Replacement or Reattachment of Lower Extremity With Major Complication and/or Comorbidity
Results: Length of Stay (LOS)

Study 2.81 (± 1.28) vs. Control 3.04 days (± 1.60), (p<0.0001)

Mean LOS difference = 0.23 days (5.5 hours)
Results: Length of Stay – *Calculation 1*

Financial Implications: What is the LOS cost savings associated with Exparel® use?

Cost savings per day reduction in LOS = $500 per day*

**Step 1:** 1287 patients in study group; mean LOS for study group 2.81 days

\[
1287 \text{ patients} \times 2.81 \text{ days} = 3616.47 \text{ patient days}
\]

**Step 2:** 1178 pts in control group; mean LOS for control group 3.04 days

\[
1178 \text{ patients} \times 3.04 \text{ days} = 3581.12 \text{ days}
\]

**Step 3:** To determine cost savings per day

\[
3616.47 - 3581.12 \text{ patient days} \times \frac{\text{cost savings}}{\text{day}} = 35.35 \text{ patient days} \times \frac{\text{cost savings}}{\text{day}}
\]

\[
= $17,675 \text{ savings achieved by LOS reduction within our 4 month study data}
\]

**Step 4:** Annualized cost savings

\[
$17,675 \text{ cost savings within our 4 months study data} \times 3
\]

\[
= $53,025 \text{ annual cost savings achieved by LOS reduction}
\]
Results: Length of Stay – *Calculation 1*

**Financial Implications:** What are the overall healthcare costs associated with these Exparel® cases?

**Step 1:** # of patients received Exparel® in FY2014

\[ \frac{12,498 \text{ patients}}{\text{FY2014}} \times 52\% \text{ Exparel Usage pattern} = 6,499 \text{ patients who received Exparel} \]

**Step 2:** Cost of Exparel® in comparison to SOC* for FY 2014

\[ 6,499 \text{ patients} \times \$294.15 \text{ DRG based drug costs per case diff} = \$1,911,680.85 \text{ ($1.9 million)} \]

**Step 3:** Overall healthcare costs associated with Exparel® use

\[ \$1,911,680 \text{ Cost of Exparel in FY2014} - \$53,025 \text{ Annual LOS reduction cost saving} \]

\[ = \$1,858,655 \text{ ($1.86 million)} \]

* SOC = Standard of care: patients in control group NOT receiving Exparel®
Results: Length of Stay – *Calculation 2*

**Clinical Significance:** How many patients can get discharged earlier by one day?

Estimated 65 patients in 1264 patient sample size (5.1%) could be discharged one day sooner

*One in every 19 patients*

19 patients receiving Exparel® for DRG 469/470
Results: Length of Stay – *Calculation 2*

Financial Implications: What are the overall healthcare costs associated with these Exparel® cases?

\[
\text{Cost for Exparel in 19 pts} - \text{Cost savings for reducing LOS by 1 day} - \text{Cost for SOC* in 19 patients} \]

\[
\text{Cost difference} = $2506.85
\]

**Annualized cost difference: $500,314.48£**

*Based on CHS FY2013 acute care hospitalization data: Operation expenses include salaries & wages, benefits, contract labor, supplies, medical spec fees, purchased services, physician recruiting, repairs & maintenance, marketing, utilities, prop taxes & ins., HITECH incentives, rent, equity & earn – uncon subs and other operating expenses

£Patient utilization calculated based on 4 months study period: n=1287 for 4 months; n=3861 for 12 months

* SOC = Standard of care: patients in control group NOT receiving Exparel®
Results: Length of Stay

What are the overall healthcare costs associated with these Exparel® cases?

Summary:
• FY2014, as an enterprise, CHS spent $1.9 million for Exparel® in DRG 469/470 alone
• There is $53,025 – $500,314 annualized cost savings due to LOS reduction associated with Exparel® use

The overall health care costs associated with Exparel® use for FY2014 was $1.41 to 1.86 million with considerations of LOS reduction cost savings based on the two calculation models.
# Results: Total Analgesic Consumption

## Oct. 2014 data (n=776)

### Average Total Analgesic Consumption per Patient Day (mg/day)

<table>
<thead>
<tr>
<th></th>
<th>Ofirmev</th>
<th>Acetaminophen</th>
<th>Ibuprofen</th>
<th>Ketorolac</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td>530</td>
<td>1330</td>
<td>8</td>
<td>18</td>
<td>92</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>155</td>
<td>1533</td>
<td>16</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>298 to 510</td>
<td>-365.6 to -41.2</td>
<td>-29.4 to 13.7</td>
<td>3.7 to 11.3</td>
<td>-7.1 to 11.4</td>
</tr>
</tbody>
</table>

- ANOVA statistical analysis indicates the p-value = 0.3173
- Zoom-in student’s t-test was performed to test the difference for opioid consumption, p-value = 0.6525
SUBGROUP ANALYSIS: ORTHOPEDIC CONSULTING SERVICES
## Results: Secondary Endpoints Subgroup Analysis

### Average Daily Highest Pain Intensity Score

<table>
<thead>
<tr>
<th></th>
<th>POD 0</th>
<th>POD 1</th>
<th>POD 2</th>
<th>POD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>5.9 ± 2.9 (n=121)</td>
<td>6.6 ± 2.2 (n=123)</td>
<td>5.7 ± 2.5 (n=107)</td>
<td>5.4 ± 2.6 (n=43)</td>
</tr>
<tr>
<td>Control</td>
<td>5.4 ± 2.9 (n=92)</td>
<td>6.8 ± 2.1 (n=91)</td>
<td>6.4 ± 2.5 (n=77)</td>
<td>5.7 ± 2.7 (n=35)</td>
</tr>
</tbody>
</table>

### Average Daily Distance Ambulated (feet)

<table>
<thead>
<tr>
<th></th>
<th>POD 0</th>
<th>POD 1</th>
<th>POD 2</th>
<th>POD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>95.8 ± 139.5 (n=109)</td>
<td>362.7 ± 354.1 (n=119)</td>
<td>515 ± 540.7 (n=94)</td>
<td>315.8 ± 491.5 (n=39)</td>
</tr>
<tr>
<td>Control</td>
<td>63.2 ± 110 (n=78)</td>
<td>295.8 ± 322.6 (n=90)</td>
<td>446.2 ± 525 (n=78)</td>
<td>337.3 ± 495.5 (n=35)</td>
</tr>
</tbody>
</table>

* Insufficient power to detect difference

£ Protocolized goal for ambulation distance: walk ≥ 300 feet
Study Summary

What we have learned thus far...

Quality patient care was provided to all patients

• No difference was detected in pain control and patient’s ability to recover
• The effects of Exparel® on pain score and ambulation distance could not be adequately assessed due to limited subset sample size
• No difference was observed in total analgesic consumption throughout hospitalization

Higher DRG-based drug cost per case was associated with the use of Exparel® for DRG 469/470

The effects of Exparel® use on LOS for DRG 469/470 was lower; however, the economic impact did not approach breakeven
Study Limitations & Discussions

Here are the limitations we have observed from the study:

<table>
<thead>
<tr>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient demographic data: severity of illness, comorbidities were not considered</td>
</tr>
<tr>
<td>Case-control matching was not performed (100% real world patient sample)</td>
</tr>
<tr>
<td>Total analgesic consumption was performed vs. focus only on post-operative</td>
</tr>
<tr>
<td>analgesic consumption</td>
</tr>
<tr>
<td>Adverse event monitoring data were not collected</td>
</tr>
<tr>
<td>Use of femoral nerve block or adductor canal block was not assessed \ variability</td>
</tr>
<tr>
<td>of surgical protocol</td>
</tr>
<tr>
<td>DRG-based drug costs per case limitation</td>
</tr>
</tbody>
</table>

Study results do not detect clinical advantages to support the use Exparel® for patients with DRG 469/470
Formulary Approach for the Management of Liposomal Bupivacaine Pharmacotherapy Costs

Community Health Systems
Formulary Management Strategy
How formulary management works at Community Health Systems

Enterprise-wide formulary and formulary process
- Single, centralized Formulary Management Committee (FMC)
  - Establishes formulary category status of medications
    - Category A – Eligible for local Pharmacy and Therapeutics Committee (P&T) decision
      - May be associated with restriction
    - Category B – May be approved on a case-by-case basis; not eligible for local P&T decision
      - May be associated with usage criteria
    - Category C – Appeals process needed for ordering medication; not eligible for local P&T decision
  - Local hospital formularies may be maintained an integrated formulary through their local P&T and Medical Executive Committees
    - May be more restrictive
  - Physicians may appeal FMC decisions through written process including primary literature documentation
Liposomal Bupivacaine—Formulary Management Strategy

Originally reviewed in April 2014

• Assigned a Category Status of Category B (May be approved on a case-by-case basis; not eligible for local P&T decision)
  — Usage Criteria: Marshall Steele Orthopedic Program AND setting of Total Knee Arthroplasty ONLY

• Enterprise-wide appeals process
  — Two appeals thus far
Orthopedic Consulting Services

How did this enter the picture?

Focus on:
- Best practice protocols
- Quality outcomes
- Care team coordination
- Outcome measurement
- Improved standardization
Challenges

What is impacting our strategy?

• Resolution of FDA Legal Action:
  — Administration at surgical site is NOT limited to any specific surgery type or site
    • Total hip arthroplasty?
    • Spinal surgery?
    • Shoulder surgery?
    • Bariatric surgery?
    • Other gastrointestinal surgeries?
    • Reconstructive breast surgery?

• Orthopedic consulting services
• Impact on other medications
• Impact of administration technique on results
• Marketing
Opportunities
What else could we do?

• Implement further restrictions of liposomal bupivacaine
• Improvement in standardization of standard of care
• Orthopedic consulting services
• Explore alternatives
  — Cocktails
## Joint Cocktails

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Cocktail</th>
<th>Surgical Procedure</th>
<th>Sample Size</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snyder et al. (2016)</td>
<td>Ketorolac 30 mg Morphine PF 5 mg Ropivacaine 400 mg</td>
<td>Total knee arthroplasty</td>
<td>N = 70</td>
<td>Liposomal bupivacaine was associated with lower pain scores in both the PACU (M = 2.11 vs 3.49; p &lt; M 0.05) and postoperatively (p &lt; 0.05 for POD #1 and p &lt; 0.01 for POD#2), less narcotics administration in the PACU and post-operatively (p &lt; 0.01 for PACU and p &lt; 0.01 for POD#2), and higher patient satisfaction with in-hospital pain control and pain control overall was high in the liposomal bupivacaine group (p &lt; 0.01 and p &lt; 0.0001)</td>
</tr>
<tr>
<td>Collis et al. (2016)</td>
<td>Ropivacaine 246.25 mg Epinephrine 0.5 mg Ketorolac 30 mg Clonidine 0.08 mg</td>
<td>Total knee arthroplasty</td>
<td>N = 105</td>
<td>Similar with respect to pain levels, narcotic usage, and range of motion</td>
</tr>
<tr>
<td>Yu et al. (2016)</td>
<td>Bupivacaine 10 mg Morphine 5 mg Ketorolac 30 mg</td>
<td>Total hip arthroplasty</td>
<td>N = 1272</td>
<td>Liposomal bupivacaine was associated with lower total narcotic use (p &lt; 0.001), higher achievement of physical therapy goals (p &lt; 0.001), and a reduction in length of stay by 0.31 days (p &lt; 0.001)</td>
</tr>
<tr>
<td>Heim et al. (2015)</td>
<td>Ropivacaine Epinephrine Ketorolac (no doses provided)</td>
<td>Total knee arthroplasty</td>
<td>N = 50</td>
<td>Liposomal bupivacaine was associated with lower pain scores (p &lt; 0.001), shorter hospital stay (p &lt; 0.0001), and greater walking distance on post-operative day 1 (p &lt; 0.001)</td>
</tr>
</tbody>
</table>
Conclusions

• Would like to implement further restriction
  — Further research required?
  — Potential changes with accountable care?
• Develop true standard of care
• Continue to evaluate use of cocktails
References


Questions?

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