Use of Intravenous Acetaminophen to Control Pain and Improve Outcomes in Thoracic Surgery

Mehul Patel1, Naveen Jayakumar1, Kian Bagheri2, Kaveh Bagheri2 and Ara S. Klijian1*

1Department of Thoracic Surgery, Sharp and Scripps Hospitals, USA
2Department of Critical Care and Pulmonary Medicine, Sharp Grossmont Hospital, USA
3Department of Internal Medicine, Eisenhower Health, Rancho Mirage, CA, USA
4University of Michigan, USA

Abstract

Objective: The primary objective was to assess whether the addition of IV acetaminophen (Ofirmev) to standard opioid and ketorolac pain relievers for thoracotomy, Video Assisted Thoracic Surgery (VATS), and Awake Video Assisted Thoracic Surgery (AVATS) patients reduced ICU length of stay (LOS), time to extubation, hospital LOS, or opioid use. The secondary outcomes evaluated were reintubation, patient satisfaction and pain index. We also looked at the occurrence of ileus, pneumonia, Deep Venous Thrombosis (DVT), Pulmonary Emboli (PE), Urinary Tract Infection (UTI), Atrial Fibrillation (AF), IV phlebitis, and development of delirium.

Methods: This was a retrospective cohort study conducted in adults who had undergone traditional thoracotomies, VATS, and AVATS procedures between 2012 to 2018 at two academic centers. We evaluated 199 cases. There were 98 patients who received only opioids and ketorolac (OK) and 101 patients who received IV acetaminophen in conjunction with opioid and ketorolac and (OK+A). Patients who did not receive IV Tylenol did so do to lack of availability of IV Tylenol at location/time of surgery. Treatment groups were not randomized. All procedures were performed by a single surgeon.

Results: Analysis included all 199 patients. The average LOS, in days, for the OK+A group was 2.33 (95% CI 2.16 - 2.49) after VATS, 1.53 (95% CI 1.37 - 1.69) after AVATS, and 3.57 (95% CI 3.31 - 3.82) after thoracotomy, respectively. In contrast, for the comparator group receiving traditional pain relievers, mean LOS values were 2.95 (95% CI 2.80 - 3.10), 2.45 (95% CI 2.17 - 2.73), and 5.16 (95% CI 4.64 - 5.677). The average time to extubation (hours) for these procedures in the OK+A group was 0.33 (95% CI 0.15 - 0.52) for VATS and 1.30 (95% CI 0.94 - 1.66) for thoracotomy, versus, in the traditional group, 8.37 (95% CI 4.36 - 12.39) for VATS and 18.13 (95% CI 15.69 - 20.56) for thoracotomy. The average ICU LOS (in days) for the OK+A group was 0.51 (95% CI 0.42 - 0.60) for VATS, 0.36 (95% CI 0.25 - 0.46) for AVATS, and 1.47 (95% CI 1.34 - 1.60) for thoracotomy. In contrast, for the traditional group, the ICU LOS was 1.14 (95% CI 1.01 - 1.27) for VATS, 1.39 (95% CI 1.19 - 1.59) for AVATS, and 2.36 (95% CI 1.90 - 2.82) for thoracotomy. We saw a trend towards decreased opioid use in patients receiving IV acetaminophen compared to the traditional regimen.

Conclusion: In this non-randomized cohort, addition of IV acetaminophen to traditional pain management with opioids and ketorolac for both thoracoscopic surgeries and open thoracotomy led to clinically significant decreases in the average hospital LOS, time to extubation, and ICU LOS. This effect was most marked in patients having AVATS. Integrating routine IV acetaminophen usage in patients undergoing thoracic surgery was associated with improved patient comfort and satisfaction, and helped improve compliance with incentive spirometry, earlier ambulation, and lower urinary catheter dependence. This would be expected to reduce complications such as pneumonia, DVT, PE, and UTI. The demonstrated reduced LOS should also translate to improved hospital cost saving.

Keywords: IV acetaminophen; Ofirmev; Thoracotomy; VATS; AVATS; Multimodal analgesia

Background

Thoracic surgery can lead to nociceptive, neuropathic, and referred pain, which can make managing pain difficult following thoracic surgeries [1]. Pain in thoracic surgeries can lead to
provide minimal clinical benefits and the potential cost outweighs
post-cardiac surgery patients; they concluded that IV acetaminophen
does not reduce opioid consumption [6]. Douzjian and Kulik et al.
that IV acetaminophen can reduce pain after cardiac surgery but
decrease PACU stay [5]. Other small studies have also suggested
pain in the post-procedure period. However, the adverse effects of
opioids on respiratory depression, Gastrointestinal (GI) motility,
and delirium make it difficult to balance patient’s analgesia with
avoiding adverse events. Such adverse events lead to increased ICU
time, hospital stay, re-intubations, and hospital-associated infections.
Inadequate analgesic control can lead to decreased mobility, which
can increase the risk for DVTs, PE, and UTIs. These adverse events
and inadequate pain control can increase healthcare costs and place
unnecessary burden on the healthcare system. Integrating non-
opioid analgesia is increasingly becoming important, especially as
opioid abuse and opioid overdose is increasing. Newer modalities
have become available to manage pain in patients undergoing
toracoscopic surgery, including thoracic epidural analgesia, paravertebral
analgesia, and intrathecal opioids [1]. However, these all rely on use
of opioids. NSAIDs have also been shown to be beneficial to help
reduce pain and opioid requirement in thoracotomy [1]. However,
NSAIDs in the elderly are associated with acute renal failure and GI
bleed.

Small studies have suggested that IV acetaminophen does not
decrease PACU stay [5]. Other small studies have also suggested
that IV acetaminophen can reduce pain after cardiac surgery but
does not reduce opioid consumption [6]. Douzjian and Kulik et al.
performed a nine-article database review of the routine use of IV
acetaminophen when added to a background of opioid therapy in
post-cardiac surgery patients; they concluded that IV acetaminophen
provided minimal clinical benefits and the potential cost outweighs
the benefits [2]. However, currently there are no clear studies that
examine the role of IV acetaminophen in post thoracotomy, VATS,
and AVATS patients. Here we examine the effect of IV acetaminophen
on hospital length of stay, time to extubation, ICU length of stay,
opioid use, and pain index in patients after thoracotomies, VATS,
and AVATS. In this study we use a multimodal approach for thoracic
procedures, with the use of IV acetaminophen prior to incision, in
combination with NSAID and opioids.

Methods

We extracted data from two academic centers for patients who
had undergone thoracotomy, VATS, and AVATS. The specific types
of procedures we looked at were: lobectomy, segmentectomy, wedge
resection, decortication, pericardial window, bronchopulmonary
fistula repair, and esophageal perforation repair. All procedures
were performed between 2012 and 2018 by a single surgeon (author
A. Klijian). This was a nonrandomized, retrospective chart review
cohort study. We analyzed patients who had undergone the above
procedures and looked at patients who received IV acetaminophen
in conjunction with opioid and ketorolac (OK+), and those who
received only opioids and ketorolac (OK+A). Post-procedure patients in both groups were given a standard
opioid protocol of 2 mg IV morphine sulfate and 0.5 mg of IV
hydromorphone, while those in the IV acetaminophen group also
received 1 g IV acetaminophen prior to skin incision, followed by 1
gram every 6 hr as needed to a maximum of 36 hr. All patients, except
for five with renal insufficiency in the IV acetaminophen arm and

![Figure 1: Scatter plot comparing average hospital length of stay (diamond, in bold) in days between IV acetaminophen and traditional pain management. Error bars from the mean show 95% confidence intervals. VATS - video-assisted thoracoscopic surgery; AVATS - Awake Video-Assisted Thoracoscopic Surgery.](image1)

![Figure 2: Scatter plot comparing average time to extubation (Diamond, in bold) in hours between the different groups. Error bars from the mean show 95% confidence intervals.](image2)

![Figure 3: Scatter plot comparing average length of stay in ICU (diamond, in bold) in days between IV acetaminophen and traditional pain management. Error bars from the mean show 95% confidence intervals. VATS - video-assisted thoracoscopic surgery, AVATS - Awake video-assisted thoracoscopic surgery.](image3)
**Table 1: Distribution of patients between the two groups.**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>IV acetaminophen</th>
<th>Traditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracotomy</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>VATS</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>AVATS</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>98</td>
</tr>
</tbody>
</table>

VATS: Video-assisted Thoracoscopic Surgery; AVATS: Awake Video-assisted Thoracoscopic Surgery

**Table 2: Patient Demographics and Comorbidities.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IV acetaminophen</th>
<th>Traditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (Males/females)</td>
<td>101 (52/49)</td>
<td>98 (48/50)</td>
</tr>
<tr>
<td>Average Age, (years)</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Essential Hypertension</td>
<td>51%</td>
<td>47%</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Note that IV acetaminophen group had higher percentage of co-morbidities

There were 199 cases evaluated. There were 101 patients who received IV acetaminophen in combination with opioids and ketorolac, and 98 patients who received only opioids and ketorolac (Table 1). Primary outcomes were time to extubation, ICU Length of Stay (LOS), hospital LOS, and total opioid use. Secondary outcomes evaluated included rates of reintubation, patient satisfaction, and pain index. We also looked at the occurrence of ileus, pneumonia, DVTs, PE, UTI, atrial fibrillation, IV phlebitis, and development of delirium.

**Results**

**Patients and treatment**

A total of 199 patient charts were analyzed retrospectively from two academic centers. Baseline demographic data and comorbidities were well balanced between the two groups (Table 2). Out of the 199 patients, 101 received IV acetaminophen, and 98 underwent traditional opioid-based analgesic regimen. Similar to the balanced demographic data, specific procedures performed (i.e. lobectomy, segmentectomy etc.) were also relatively well-distributed between the two groups (supplementary data, Tables S1 and S2).

**Outcomes**

The average LOS in days for the IV acetaminophen group for VATS, AVATS, and thoracotomies was 2.33 (95% CI 2.16 - 2.49), 1.53 (95% CI 1.37 - 1.69), and 3.57 (95% CI 3.31 - 3.82) respectively. For the traditional group, the mean LOS was 2.95 (95% CI 2.80 - 3.10), 2.45 (95% CI 2.17 - 2.73), and 5.16 (95% CI 4.64 - 5.677) for VATS, AVATS and thoracotomies respectively. As demonstrated in Figure 1, the average length of stay was significantly lower for the IV acetaminophen groups in comparison to traditional opioid-based regimens. A similar statistically significant trend was noted for extubation time, with the exception that AVATS was not included in the data analysis since these patients were not mechanically ventilated during or after the procedure (Figure 2). The average time to extubation (hours) for these procedures was 0.33 (95% CI 0.15 - 0.52) for VATS and 1.30 (95% CI 0.94 - 1.66) for thoracotomy in the IV acetaminophen group and 8.37 (95% CI 4.36 - 12.39) for VATS and 18.13 (95% CI 15.69 - 20.56) for thoracotomy for the traditional opioid-based regimen. We also performed similar statistical analysis for ICU LOS for the traditional pain management and found the IV acetaminophen group had statistically significant lower values (Figure 3). The average ICU LOS (in days) for the IV acetaminophen group was 0.51 (95% CI 0.42 - 0.60) for VATS, 0.36 (95% CI 0.25 - 0.46) for AVATS, and 1.47 (95% CI 1.34 - 1.60) for thoracotomy. For the traditional group the ICU LOS was 1.14 (95% CI 1.01 - 1.27) for VATS, 1.39 (95% CI 1.19 - 1.59) for AVATS and 2.36 (95% CI 1.90 - 2.82) for thoracotomy.

**Pain control**

To investigate if the pain control was affected by using IV acetaminophen vs. the traditional method, we also compared the Visual Analogue Pain scale and patient satisfaction scores (0-100%) between the two groups. Unfortunately, we could not calculate statistical significance for this data group, since the raw data was not available for analysis. Overall, we found improved pain scores and increased patient satisfaction scores (Table 3).

**Adverse events**

We compared the incidence of adverse events between the two treatment groups and found them to be lower in the IV acetaminophen group. The only adverse events noted in this group were 3 cases of uncomplicated atrial fibrillation compared with 2 cases in the traditional control group. However, more compellingly, in the traditional opioid-based pain management group, there were 4 incidences of ileus, 3 occurrences of pneumonia, 1 case of deep vein thrombosis, 2 occurrences of urinary tract infections, 2 episodes of atrial fibrillation, one occurrence of IV phlebitis, 4 occurrences of mild delirium, 4 occurrences of moderate delirium, and 1 case
Ara S. Klijian, et al., Clinics in Surgery - Thoracic Surgery

It is important to note (Table 4) that there was a trend towards decreased opioid use in patients receiving IV acetaminophen. Patients who did not receive IV acetaminophen required additional doses of morphine and hydromorphone when undergoing VATS, AVATS, and thoracotomy. For instance, 80% of the patients who underwent video assisted thoracoscopic surgery in the IV acetaminophen group had lower adverse events such as ileus, pneumonia, DVT, UTI, delirium, and reintubation. There were also improved pain control and patient satisfaction in the IV acetaminophen group. Patients in the traditional group had more complications, such as respiratory depression and ileus. Previous studies have looked at a multimodal post-operative pain management approach in which acetaminophen is combined with centrally-acting opioids for synergistic pain relief after surgery [7]. A systematic review by Douzjian et al. [10] evaluated the use of IV acetaminophen in combination with opioids in post-cardiac surgery patients and found mixed results for reduction in pain, opioid consumption, and improvement in pulmonary function, and incidence of nausea and vomiting [2]. Its benefits for pain control were marginal at best. However, Tsourtzopoulou et al. [8] noted that surgical patients who received a single dose of IV acetaminophen experienced effective post-operative analgesia for 4 hr, which was associated with a 30% reduction in opioid consumption over 4 hr.

In this study we assessed the use of IV acetaminophen status-post thoracotomy, VATS, and AVATS to see its effects on ICU length of stay, time to extubation, hospital length of stay, and opioid use. In this retrospective study we evaluated patients who received pre-emptive IV acetaminophen in conjunction with opioids and those who received only traditional opioids. Pre-emptive IV acetaminophen followed by prn use of IV acetaminophen led to clinically significant decrease in the average length of stay when compared to traditional opioid-based regimens. There was a statistically significant trend also noted for extubation time, with the exception of AVATS. The IV acetaminophen group also had statistically significant lower values for ICU LOS. There were also improved pain control and patient satisfaction in the IV acetaminophen group. Patients in the IV acetaminophen group had lower adverse events such as ileus, pneumonia, DVT, UTI, delirium, and reintubation. There were more cases of uncomplicated atrial fibrillation in the IV acetaminophen group. The exact reason for this is unclear.

Discussion

Control of pain after thoracic surgery can be difficult. As noted above, inadequate pain control leads to decreased mobility, with increased risk for DVTs, PE, and UTIs. Opioids have generally been the mainstay treatment, but adverse events associated with opioid use include respiratory depression and ileus. Previous studies have looked at a multimodal post-operative pain management approach in which acetaminophen is combined with centrally-acting opioids for synergistic pain relief after surgery [7]. A systematic review by Douzjian et al. [10] evaluated the use of IV acetaminophen in combination with opioids in post-cardiac surgery patients and found mixed results for reduction in pain, opioid consumption, and improvement in pulmonary function, and incidence of nausea and vomiting [2]. Its benefits for pain control were marginal at best. However, Tsourtzopoulou et al. [8] noted that surgical patients who received a single dose of IV acetaminophen experienced effective post-operative analgesia for 4 hr, which was associated with a 30% reduction in opioid consumption over 4 hr.

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It is important to note that this was a single center non-randomized study, which is a weakness of this study. Further studies are needed to validate the pre-emptive use of IV acetaminophen and its regularly scheduled use after thoracic procedures. In this study we implemented a balanced analgesia approach, but there were no strict guidelines on the dosing of the IV acetaminophen in the post-op period. The results from this study do suggest that IV acetaminophen can play a significant role in thoracic surgical procedures as part of a multimodal analgesic approach to help pain control, decrease opioid use, and improve overall outcomes.

Conclusion

Use of IV acetaminophen routinely in conjunction with traditional pain management for both thoracoscopic surgery and open thoracotomy led to significant decreases in the average hospital length of stay, time to extubation, and ICU length of stay, with best results seen in the patients having AVATS with IV acetaminophen use. AVATS has been shown to improve outcomes compared to traditional VATS cases [3,9-11] combined with use of IV acetaminophen obtained best results. Integrating routine IV acetaminophen usage in patients undergoing thoracic surgery also improves patient comfort and satisfaction, helping to improve compliance with incentive spirometry usage, earlier ambulation, and lower urinary catheter dependence. This in turn minimized complications such as pneumonia, DVT, PE, and UTI. These improvements are expected to translate to improved hospital cost savings.

Financial Disclosures

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References