



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

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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

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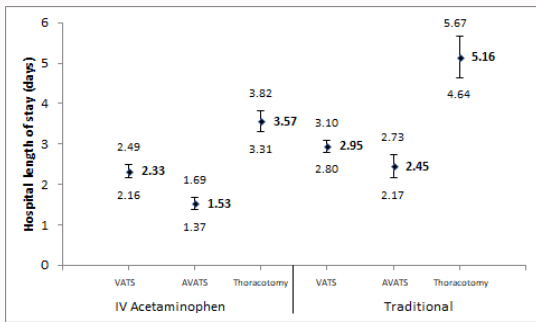


Figure 1: Scatter plot comparing average hospital length of stay (diamond, in bold) in days between IV acetaminophen and traditional pain management. Error bars from the mean show 95% confidence intervals. VATS - video-assisted thoracoscopic surgery; AVATS - Awake Video-Assisted Thoracoscopic Surgery.

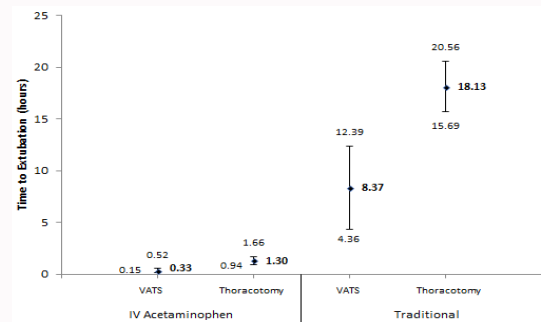


Figure 2: Scatter plot comparing average time to extubation (Diamond, in bold) in hours between the different groups. Error bars from the mean show 95% confidence intervals.

respiratory splinting which can increase the risks of atelectasis and development of pneumonia in patients. Poor pain control is associated with increased catecholamine release, which can trigger myocardial infarction, strokes, and bleeding complications [2]. This has led to increased emphasis on controlling pain following surgical procedures. Optimal pain-controlling strategies remain a challenge for many surgeons, even in minimally invasive pain sparing thoracic surgical techniques, such as Awake Video-Assisted Thoracic Surgery (AVATS), which has been shown to be safe in complex thoracic surgery with equal or improved outcomes without compromise in safety [3].

For over two decades, multimodal or balanced pain strategies have been researched with the goal of combining analgesics from different pharmacologic groups with differing mechanisms of action with additive or synergistic effects to improve analgesia efficacy and safety [4]. Opioid analgesia has traditionally been used to manage 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 thoracic 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. [2] 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

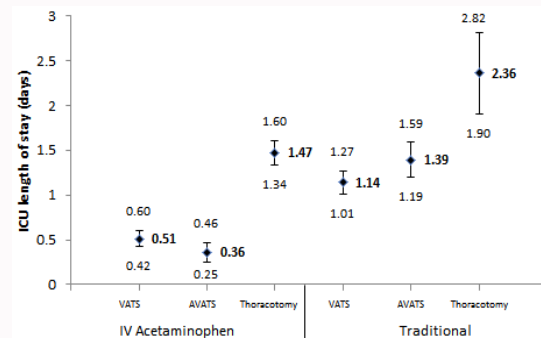


Figure 3: Scatter plot comparing average length of stay in ICU (diamond, in bold) in days between IV acetaminophen and traditional pain management. Error bars from the mean show 95% confidence intervals. VATS - video-assisted thoracoscopic surgery, AVATS - Awake video-assisted thoracoscopic surgery.

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+A), and those who received only opioids and ketorolac (OK, traditional treatment group). 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

Table 1: Distribution of patients between the two groups.

Procedure	IV acetaminophen	Traditional
Thoracotomy	21	20
VATS	31	32
AVATS	49	46
Total	101	98

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

Table 2: Patient Demographics and Comorbidities.

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

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

four patients in the traditional arm with renal insufficiency received 15 mg IV ketorolac every 8 hours for a total of three doses in both VATS and AVATS groups and 15 mg IV ketorolac every eight hours for a total of six doses in the thoracotomy group in both arms. We looked at how much additional opioid were required in both groups.

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 regiment. 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

Table S1: Case types of IV acetaminophen group.

Procedure	Thoracotomy	VATS	AVATS	Total
Lobectomy	8	18	10	36
Segmentectomy	2	4	4	10
Wedge Resection	0	2	18	20
Decortication	9	5	10	24
Pericardial Window	0	1	5	6
Bronchopleural Fistula Repair	1	0	1	2
Esophageal Perforation Repair	1	0	1	2

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

Table S2: Case types of the traditional group.

Procedure	Thoracotomy	VATS	AVATS	Total
Lobectomy	8	16	10	34
Segmentectomy	3	3	5	11
Wedge Resection	0	4	14	18
Decortication	8	8	12	28
Pericardial Window	0	1	3	4
Bronchopleural Fistula Repair	0	0	1	1
Esophageal Perforation Repair	1	0	1	2

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

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

Table 3: VAS Pain Index / Patient satisfaction scores for both groups.

	IV acetaminophen			Traditional		
	Thora	VATS	AVATS	Thora	VATS	AVATS
Lobectomy	3/92	2/95	1/97	9/80	6/90	5/92
Segmentectomy	2/94	1/96	1/98	10/80	8/89	7/91
Wedge Resection	-	1/97	1/100	-	8/90	7/92
Decortication	3/92	2/93	2/95	10/80	6/88	7/90
Pericardial Window	-	1/98	0/100	-	2/90	2/92
BPF Repair	2/92	-	1/96	-	-	5
EP Repair	3/90	2/94	2/96	10/75	-	8/82

Thora: Thoracotomy; VATS: Video-assisted Thoracoscopic Surgery; AVATS: Awake Video-assisted Thoracoscopic Surgery; BPF: Bronchopleural Fistula Repair; EP: Esophageal Perforation. Data was unavailable for certain groups, cells indicated as “-”

Table S3: Breakdown of adverse events in the subgroups.

	IV acetaminophen	Traditional
Illeus	None	1 Thoracotomy Decortication 1 VATS decortication 1 Thoracotomy Lobectomy 1 Thoracotomy EP
Pneumonia	None	1 VATS Lobectomy 1 Thoracotomy Segmentectomy 1 Thoracotomy Decortication
DVT	None	1 Thoracotomy Segmentectomy
PE	None	None
UTI	None	1 Thoracotomy Segmentectomy 1 AVATS Lobectomy
Afib	1 VATS Pericardial window 1 AVATS Segmentectomy 1 Thoracotomy Decortication	1 VATS Pericardial Window 1 AVATS Lobectomy
Phlebitis	None	1 AVATS segmentectomy
Mild Delirium	None	1 VATS Decortication 1 VATS Lobectomy 2 VATS EP repair
Moderate Delirium	None	1 Thoracotomy Segmentectomy 1 Thoracotomy EP Repair 1 Thoracotomy Lobectomy 1 Thoracotomy Decortication
Reintubation	None	1 Thoracotomy EP Repair

Thora: Thoracotomy; VATS: Video-assisted Thoracoscopic Surgery; AVATS: Awake Video-assisted Thoracoscopic Surgery; BPF: Bronchopleural Fistula Repair; EP: Esophageal Perforation; DVT: Deep vein thrombosis; PE: Pulmonary Embolism; UTI: Urinary Tract Infection; Afib: Atrial Fibrillation

requiring reintubation. Breakdown of the types of procedures are available in the supplemental data section (Table S3).

Opioid usage

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 thoracoscopy in the IV acetaminophen group received morphine sulfate, and 82% of patients in the traditional group required morphine, however those in the traditional group required 5 additional doses of morphine when compared to the IV acetaminophen group. While statistical significance of this trend could not be established, this trend was important to note (Table 4).

Table 4: Opioid Usage between the two groups.

		IV acetaminophen	Traditional
VATS	Morphine 2mg	80% ^a	82% ^b
	Dilaudid 0.5mg	20%	18% ^c
AVATS	Morphine 2mg	85%	70% ^d
	Dilaudid 0.5mg	15%	30% ^e
Thoracotomy	Morphine 2mg	78% ^f	85% ^g
	Dilaudid 0.5mg	22% ^h	15% ⁱ

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

a only 1 patient required 2 additional doses

b 80% of these patients required 5 additional doses

c 20% of these patients required 6 additional doses

d 72% of these patients required 3 additional doses

e 28% of these patients required 4 additional doses

f 90% of these patients required 2 additional doses

g 75% of these patients required 12 additional doses

h 10% of these patients required 2 additional doses

i 15% of these patients required 8 additional doses

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, Tzortzopoulou 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. There was a trend towards decreased opioid use in patients receiving IV acetaminophen. While it is important to note that statistical significance for opioid reduction, pain control, and patient satisfaction was not established, the trends were favorable.

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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