Original Article

Is P&T Ready to Add Rapid Cycle Analytics to Formulary?

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Abstract

Purpose: The intent of this article is to evaluate a novel approach, using rapid cycle analytics and real world evidence, to optimize and improve the medication evaluation process to help the formulary decision making process, while reducing time for clinicians. **Summary:** The Pharmacy and Therapeutics (P&T) Committee within each health system is responsible for evaluating medication requests for formulary addition. Members of the pharmacy staff prepare the drug monograph or a medication use evaluation (MUE) and allocate precious clinical resources to review patient charts to assess efficacy and value. We explored a novel approach to evaluate the value of our intravenous acetaminophen (IV APAP) formulary admittance. This new methodology, called rapid cycle analytics, can assist hospitals in meeting and/or exceeding the minimum criteria of formulary maintenance as defined by the Joint Commission Standards. In this particular study, we assessed the effectiveness of IV APAP in total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures. We assessed the correlation to same-stay opioid utilization, average length of inpatient stay and post anesthesia care unit (PACU) time. **Conclusion:** We were able to explore and improve our organization's approach in evaluating medications by partnering with an external analytics expert to help organize and normalize our data in a more robust, yet time efficient manner. Additionally, we were able to use a significantly larger external data set as a point of reference. Being able to perform this detailed analytical exercise for thousands of encounters internally and using a data warehouse of over 130 million patients as a point of reference in a short time has improved the depth of our assessment, as well as reducing valuable clinical resources allocated to MUEs to allow for more direct patient care. This clinically real-world and data-rich analytics model is the necessary foundation for using Artificial or Augmented Intelligence (AI) to make real-time formulary and drug selection decisions

Keywords

formulary management/P&T, benchmarking, drug/medical use evaluation, data analytics, real world evidence, rapid cycle analytics

Introduction

The Pharmacy and Therapeutics (P&T) Committee within each health system is responsible for evaluating medication requests for formulary addition and subsequently assessing the downstream impact of such decisions or changes to the status of medications added to formulary. Several methods of review and committee presentations have historically been utilized, namely drug-specific monographs prepared by the health system's department of pharmacy. A committee decision is made after considering the clinical benefit, safety profile, and financial impact (ie, value). After formulary admittance, medication use evaluations (MUEs) are frequently conducted at pre-defined timeframes to justify or evaluate the committee's decision on controversial or high-cost medications.

In understanding the limitations of traditional MUE-based assessments, we explored a novel approach to evaluate the value of our intravenous acetaminophen (IV APAP) formulary admittance and validated the methodology by comparing our utilization and outcomes against an index of comparable hospitals. We utilized a new method of medication evaluation and formulary maintenance called rapid cycle analytics, which is a process that assists hospitals in meeting and/or exceeding the minimum criteria of formulary maintenance as defined by the Joint Commission Standards.[1] Rapid cycle analytics leverages available data to quickly determine whether an intervention or process change is effective. Literature supports using these novel data evaluation approaches in the development and enhancement of pharmacy services.[2] We partnered with Agilum™ to organize and normalize select IV APAP data from our organization, pertaining to our assessment of the effectiveness of IV APAP in total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures. We assessed the correlation to same-stay

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Table 1. Baseline Demographics New York Univsersity Langone Health (NYULH).

Total encounters (7501)	
Age, mean (SD) years	65 (10.4)
Sex, female	4600 (61%)
Hip procedure (%)	3728 (50%)
Inpatient	3702 (99%)
Outpatient	26 (1%)
Knee procedure (%)	3773 (50%)
Inpatient	3726 (99%)
Outpatient	47 (1%)
Opioid utilization (%)	4760 (63%)
Hip procedure	2224 (47%)
Knee procedure	2536 (53%)
IV acetaminophen utilization (%)	1595 (21%)
Hip procedure	60 (4%)
Knee procedure	1535 (96%)

Note. Table 1 provides a breakdown of the total encounters. IV = intravenous.

opioid utilization, average length of inpatient stay, and post-anesthesia care unit (PACU) time. The intent of this study was to explore and improve our organization's approach to evaluating medications by partnering with a leading external analytics expert for a more robust internal assessment, thereby leveraging significantly larger external data and real-world evidence (RWE) as a point of reference, all while performing the analysis in a shorter, more sustainable timeframe.

Methodology

NYU Langone Health is a 4*-hospital enterprise in Manhattan, Brooklyn, and Long Island, consisting of more than 1300 beds. For the purposes of this study, Agilum™ organized and normalized all of our relevant patient data from NYU Langone Health (Tisch and Langone Orthopedic Hospital) for patients that had either a TKA or a THA as inpatient and outpatient encounters using 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) and Current Procedural Terminology (CPT) codes from January 1, 2016 to September 26, 2018. We provided Agilum™ with the endpoints and parameters we intended to investigate. Patients were included if they were 19 years of age or older and had a TKA or THA procedure. Exclusion criteria included patients who were 18 years of age or younger at the date of service, had missing gender information, had > 95th percentile morphine equivalence (MME) utilization, or had undergone a nonelective procedure based on the presence of specific diagnosis codes. This study received Investigational Review Board (IRB) approval as an exempt study. Baseline patient demographics are outlined in Table 1.

As a point of reference for internal use, a parallel analysis was also conducted using Agilum™ data to compare patients from NYULH to an external set of patients who met the above criteria. This point of reference consisted of patient visit data sourced from 10 institutions similar to NYULH (academic medical centers, urban locations, and those with a similar number of beds). Patient visits were then assigned to the IV acetaminophen "IV APAP" group or no IV acetaminophen "Non-IV APAP" group. NYULH has an opioid sparse multimodal pain management protocol for patients undergoing THA or TKA procedures. At NYULH, patients are started on a pre-operative regimen that may include nonsteroidal anti-inflammatory drugs (NSAIDs; ie, aspirin 81 mg, meloxicam) or oral APAP; an intra-operative regimen that can consist of opiate-free spinal anesthesia, IV dexamethasone, IV fentanyl, IV APAP, liposomal bupivacaine, and/or a cocktail of periarticular epinephrine/bupivacaine/ketorolac. The post-operative regimen may include tramadol, opioids, APAP, NSAIDS, and/or pregabalin.

The primary outcome of our study was to assess the morphine milligram equivalence (MME) utilization between the groups. Our secondary outcomes include length of stay (LOS) and PACU duration of time. MME was measured by converting all daily opioids administered (eg, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, or oxymorphone) into equivalent doses of morphine in milligrams and then summing the milligrams across the LOS. Length of stay was measured for inpatient visits only, as the difference in days between the admit and discharge date. Post-anesthesia care unit time was measured as the difference between admit and discharge time from the PACU (hours).

Descriptive data were analyzed using means and standard deviations. For continuous variables, we examined that the distributions were not normal, and given that the non-parametric tests have a less significance level than the parametric test, we transformed the data using log 10(x) transform. Once the data were transformed into normal distributions that met the assumptions for these tests, we utilized the analysis of variance (ANOVA; 2-way and 3-way) with Tukey Honestly Significant Difference (HSD) to test for the significance level. Post-anesthesia care unit time was analyzed using the independent *t*-test. A 2-sided *P* value of $<.05$ was considered to be statistically significant.

Agilum™ performed a parallel analysis for the selected point of reference group utilizing a data warehouse of more than 130 million patients across 50 states. NYULH does not have ownership of this external database; therefore, data review and validation were not conducted by the authors.

Results

A total of 7501 NYULH encounters were included in the study. Mean age was 65 years, with 61% females. The surgical procedures were predominantly conducted in the inpatient setting. Half of these patients received hip surgeries, while the other half received knee surgeries. Opioid utilization was observed in 63% of the total patients examined and

Table 2. Outcomes New York University Langone Health (NYULH).

	IV APAP (1595)	Non-IV APAP (5906)	*P* value
Primary outcome			
Opioid utilization, morphine equivalence in mg (SD), mean	123.4 (83)	121.3 (92.4)	.007
Secondary outcomes			
Length of stay, mean days (SD)	2.4 (1.2)	2.1 (1.2)	.001
Post-anesthesia care unit time, mean hours (SD)	4.1 (2.1)	3.9 (2.1)	.024

Note. Table 2 shows a summary of the primary and secondary outcomes. IV APAP = intravenous acetaminophen.

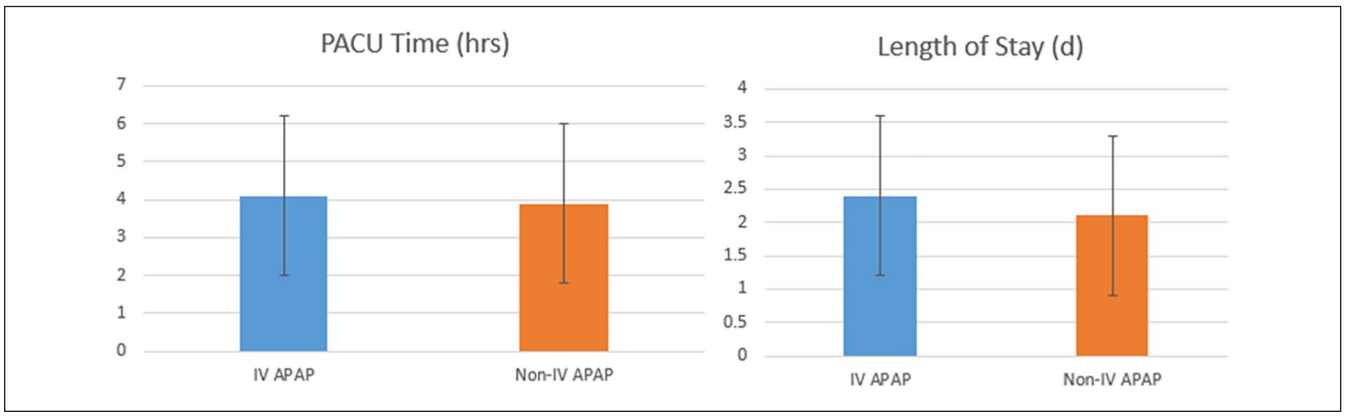

Figure 1. PACU time and mean length of stay comparison (IV APAP vs Non-IV APAP).
Note. Figure 1 compares the PACU time and mean length of stay between patients who received IV APAP and patients who did not receive IV APAP. PACU = post-anesthesia care unit; IV APAP = intravenous acetaminophen.

was more common in the knee surgery population (53%). Intravenous acetaminophen was used in only 21% of all encounters, with knee surgery patients accounting for the majority of the use (1535, 96%).

For the primary outcome, we observed a statistically significant difference in the amount of opioid MME utilization between the IV APAP group vs the non-IV APAP group. Specifically, mean opioid MME utilization was greater in the IV APAP group than the non-IV APAP group at NYULH (123.4 mg vs 121.3 mg, respectively, $P = .007$). This finding, however, was not corroborated within the reference data, in which no statistically significant difference was observed between the IV APAP and non-IV APAP groups with regard to opioid MME utilization (100.1 mg vs 99.7 mg, respectively, $P = .215$).

Intravenous acetaminophen inpatient encounters were also observed to have statistically longer mean lengths of stay than their non-IV APAP counterparts at NYULH (2.4 days vs 2.1 days, $P = .001$). Conversely, within the reference data, inpatient IV APAP encounters were observed to have statistically shorter mean LOS relative to their non-IV APAP counterparts (3.1 days vs 3.9 days, $P = .001$).

Additionally, the PACU time was observed to be statistically longer in IV APAP encounters at NYULH relative to non-IV APAP encounters (4.1 vs 3.9 hours, $P = .024$).

The practical interpretations of these results therefore suggest use of IV APAP for THA/TKA patients (1) is not associated with lower opioid MME utilization during same visit, (2) is not conclusively shown to be associated with lower mean lengths of stay, and (3) is not associated with lower mean PACU stays.

Table 2 and Figure 1 summarize our NYULH patient study outcomes.

Discussion

Intravenous acetaminophen was approved by the Food and Drug Administration (FDA) in 2010 for the treatment of mild to moderate pain, as an adjunct to opioids for the treatment of moderate to severe pain, and for the reduction of fever.[3] Pharmacokinetically, it possesses some favorable characteristics compared to oral (PO) or rectal APAP. The onset of action with IV is more rapid at 15 minutes, compared to greater than 45 minutes with PO, with a peak analgesic effect of IV administration at 1 hour. The C_{max} achieved with IV APAP is about 70% higher in the plasma and 60% higher in the cerebrospinal fluid (CSF).[4,5] Due to these attractive pharmacokinetic attributes, providers at many institutions requested the formulary addition of IV APAP.

More recently, many institutions, including NYULH, have conducted internal data analyses to evaluate the value

of this agent. Currently at NYULH, IV APAP is restricted to patients who are unable to receive PO or rectal APAP. The order must be placed by the pain management or anesthesia service for a duration of up to 24 hours. Furthermore, our orthopedic service is allowed to prescribe up to 2 doses intra-op, and 6 hours post-op, as part of a multimodal pain protocol in patients undergoing same-day surgery or with a potential for a 23-hour discharge. Data evaluating the efficacy of IV APAP as part of a multimodal pain approach in orthopedic surgeries show mixed results in relation to pain scores and opioid requirements.[6-9] Recent studies evaluating the LOS did not demonstrate a shorter LOS with IV APAP.[9-12] Additionally, recent large randomized prospective studies (Table 3) evaluating patients undergoing total hip or knee arthroplasty who received IV APAP pre-op and/or post-op compared to PO APAP showed no major difference in opioid requirements in the first 24 hours.[12-14] Hickman et al conducted the largest study to date (n = 486) that evaluated the efficacy of intraoperative IV APAP vs oral APAP in a single-centered, randomized, placebo controlled, prospective study in patients undergoing TKA or THA. They found no statistically significant difference in any of their endpoints, which included preoperative, intraoperative, or postoperative opioid use in MMEs; pain scores over 24 hours; and hospital or PACU LOS.[15]

The rapid cycle analytics method is capable of analyzing a significantly larger number of patients in a very short timeframe and provides a valuable perspective on census population and population health management based on specific parameters prioritized by the health system. Additionally, it allows the P&T committee to make data-rich and timely decisions for improved surveillance and monitoring of drugs individually, and as compared to alternative therapies.

Using a large data source allowed us to report robust findings and compare this to a real-world cohort maintained by the data warehouse from Agilum™, which contains more than 130 million patients. Having access to a large data pool allowed us to use timely and powerful internal data to further evaluate efficacy, value, and safety. As more data become available, this analysis can be easily repeated for any follow-up, providing near real-time information. This practice is a departure from the usual tedious MUEs that are performed using chart reviews to manually collect data. For instance, we recently invested 150 hours of clinician time to conduct manual chart reviews for sugammadex to determine appropriate use in 100 previously treated patients. This valuable time can be repurposed and reallocated to provide direct patient care services. Additionally, utilizing significantly larger data would have allowed us to more accurately determine the impact and value of sugammadex.

Study Limitations

NYULH has always been on the forefront of clinical and technological innovation, and we support and promote the FDA's stance that "Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions."[16] Our study is based on this premise, and we realize that this type of analysis is brand new to the industry and must be further validated to assure that our reference cohorts fully represent our study population.

Although reference cohorts provide powerful data points and can help strengthen our results, the details for the reference cohorts cannot be validated the same way your organization's data can be validated and scrutinized at this moment because you do not own the data from other organizations.

For the purpose of this particular study, we were unable to collect confounders such as severity of illness, surgical complications, and concomitant multimodal pain management (ie, liposomal bupivacaine use), which could impact or influence data interpretation; however, these are parameters that can be incorporated into future studies utilizing Agilum™ data or data available from other internal or external sources.

We did not use artificial or augmented intelligence (AI) for this study; however, this clinically RWD-rich environment and analytics model is the necessary foundation for using AI to make real-time formulary and drug selection decisions. Our methodology can measure the overall impact of a particular medication or the difference between the effectiveness of a generic versus a brand product or a biosimilar versus an innovator product in a large population. Applying AI to these datasets will make this type of evaluation possible in real-time for P&T committees, prescribers, and pharmacies. P&T committees will be able to set restrictions and protocols requiring multiple simultaneous patient-specific criteria, site of care, geography, and limitations going back as far and as broad as possible. Furthermore, having access to all these data points will help optimize predictive analysis and improve the AI portion with each encounter and data point collected.

Conclusions

Similar to prior studies, our study utilizing a significantly larger dataset found that the use of IV APAP during visits for THA/TKA procedures was not associated with decreased opioid MME utilization, shorter lengths of stay, or reduced PACU time as part of a multimodal analgesia protocol. To our knowledge, our study is the largest study to evaluate these outcomes in orthopedic TKA patients receiving IV APAP. We used real-world endpoints that can be easily translated into practice and used for formulary decision-making.

Although statistical testing on the data was conducted in such a way as to determine whether measured differences in mean values were significant regardless of direction, the operational (ie, practical) reality is that only statistically significant decreases would potentially require NYULH to re-evaluate decisions and initiatives undertaken to reduce IV APAP utilization at our facilities (eg, if IV APAP were shown to be associated with reduced opioid MME utilization). Thus,

Table 3. Evidence Regarding IV in Orthopedic Surgery (Only Includes Studies With n of 100 or More in the Last 6 Years).

Study/design	Patients	Intervention	Control	Opioid utilization/pain score (*IV vs PO for all outcomes)*	Length of Stay (*IV vs PO for all outcomes)*
O'Neal et al[13] 2017 Randomized, single-center, double-blind, placebo-controlled study	Unilateral total knee arthroplasty Postoperative analgesia (n = 174)	IV APAP 1 g (n = 57)	PO APAP 1 g (n = 58) Placebo (n = 59)	Average PACU pain score (0.56 vs 0.67, *P* = .84) Time to breakthrough pain (234 vs 245 minutes, *P* = .64) Time to rescue analgesia (*P* = .98) Total opiate consumption at 6 hours (*P* = .30) Total opiate consumption at 24 hours (*P* = .23)	Not evaluated
Politi et al[14] 2017 Randomized, prospective, single-center study	Patient undergoing hip and knee arthroplasty Multimodal perioperative analgesia (n = 120)	IV APAP 1 g preoperatively then q6h for 24 hours (n = 63)	PO APAP 1 g preoperatively then q6h for 24 hours (n = 57)	24-hour average hydromorphone equivalents given (3.71 vs 3.48 mg, *P* = .76) Hydromorphone equivalents given at each 4-hour intervals (no differences) 24-hour average VAS score (3 vs 3.4, *P* = .06) VAS score during hours 0-4 (3.4 vs 4.4, *P* = .033) VAS scores at each 4 hours interval (no differences)	Not evaluated
Hickman et al[15] 2018 Randomized, placebo-controlled, single-center, prospective equivalence study	Patients undergoing total hip or knee arthroplasty (n = 486)	IV APAP 1 g × 1 dose intraoperatively (n = 245)	PO APAP 1 g × 1 dose preoperatively (n = 241)	MME first 24 hours postoperatively (21.7 vs 21.7 mg, *P* = .60) VAS (0-10) score during hours 0-4 (3.67 vs 4.17, *P* = .90) VAS score in first 24 hours (3.4 vs 3.6, *P* = .22) Time to first pain medication (41 vs 38 minutes, *P* = .90) Postoperative nausea (53% vs 51%, *P* = .91) Postoperative vomiting (17% vs 19%, *P* = .73)	PACU LOS: 2.1 vs 2.2 hours, *P* = .17 LOS: 58.5 vs 58 hours, *P* = .63
Kelly et al[10] 2014 Retrospective case control, single center	Surgical knee procedures (n = 100)	IV APAP ×1 perioperative at least (n = 25)	Control (n = 75)	MME: 135 vs 112.5 mg (*P* = .987) MME/day: 45 vs 37.5 mg (*P* = .845)	LOS: 3 days in both groups, *P* = .799
Nwagbologu et al[12] 2016 Retrospective single-centered cohort study	Total knee arthroplasty (n = 148)	IV APAP × 1 dose at least (n = 86)	no IV APAP (n = 62)	MME at 24 hours (54.2 vs 45.4 mg, *P* = .12) MME at 48 hours (99.2 vs 79.5, *P* = .06) There was no difference in other secondary outcomes (administration of bowel regimens, antiemetics, naloxone, discharge disposition)	LOS: 3.7 vs 3.9 days, *P* = .27
Raiff et al[11] 2014 Retrospective cohort study	Hip or knee replacement (n = 176)	IV APAP × 1 intraoperative (n = 88)	Control (n = 88)	MME: 149.3 vs 147.2 mg, *P* = .904	PACU LOS: 163 vs 169 minutes (*P* = .588)

Note. IV = intravenous; IV APAP = intravenous acetaminophen; PACU = post-anesthesia care unit; MME = morphine milligram equivalence; LOS = length of stay; VAS = visual analog scale.

although the significance and sometimes the direction of the results on a particular measure may differ between NYULH and the index, the overall conclusion is still the same in that there is little to no evidence in our data that IV APAP decreases opioid MME, adjusted length of stay (ALOS), or PACU time on orthopedic visits for THA and TKA procedures.

We seek to continue building upon this innovative and novel approach of assessing the value of medication admittance decisions, as it has the potential to improve efficiency and clinical outcomes. We believe that using rapid cycle analytics to help evaluate and normalize data for formulary decisions is a big leap forward.

Declaration of Conflicting Interests

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