Title:

Hip and Knee Arthroplasty

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Key Points

1. Clinical care elements included in enhanced recovery pathways for total joint arthroplasty vary widely between institutions and geographic practice settings despite favorable outcomes.
2. Provided care is rigorously defined, delivered, and assessed, variation in details of core elements is reasonable and may be associated with successful local outcomes.
3. Multimodal analgesia, tranexamic acid and early mobilization form the basis of effective pathways for total hip- and total knee arthroplasty.
4. There remain difficulties agreeing an absolute consensus on universal enhanced recovery pathways for total hip- and total knee arthroplasty.

Abstract

Variation in care is strongly associated with variation in outcomes after total joint arthroplasty (TJA). Accordingly, much of the research into enhanced recovery efficacy for TJA has been devoted to linking standardization with better outcomes. Here we focus on recent advances suggesting that variation within a set of core protocol elements may be less important than providing the core elements themselves within enhanced recovery pathways for TJA. Provided the core elements are associated with clear benefits for patients and healthcare system outcomes, variation in the details of their provision may even contribute to the overall success of a pathway. To illustrate these concepts, we provide an updated review of literature informing: • The core pathway elements associated with optimal outcomes after THA or TKA, • The global effect of a pathway vs. the effect of individual care elements as a driver of outcomes, and • How major differences in details of core elements may be associated with minor differences in important outcomes after TJA.

Clinics Care Points

- Ensure your TJA enhanced recovery pathway includes tranexamic acid, multimodal analgesia, and early mobilization.
- Remove institutional process variation, then regularly audit compliance to each care component of your institutional enhanced recovery care pathway.
- Examine local clinical outcomes in parallel with changes to the evidence-base to identify gaps in care and opportunities to improve defined outcomes.

Introduction

Enhanced recovery pathways for total joint arthroplasty (TJA) combine best-evidence with best-practice to improve outcomes and reduce healthcare costs. Classically, clinical pathways for total hip arthroplasty (THA) and total knee arthroplasty (TKA) bundle multi-disciplinary care elements into pre-, intra- and postoperative phases (Box 1). When organized and delivered as a package of care, enhanced recovery pathways show consistent evidence of benefit for reducing morbidity, improving clinical outcomes, and shortening length of hospital stay.[1] The gains which may be achieved via enhanced recovery pathways for TJA are attributed to reducing variation in pathway content (clinical care elements) and process (delivery of care elements). Accordingly, much of the research into enhanced recovery efficacy for TJA has been devoted to linking standardization of care with better outcomes.

It is evident that process and content variation are viewed differently in enhanced recovery research and practice: Whereas variation in process is classically regarded as an opportunity to improve outcomes, variation in clinical content is frequently interpreted as evidence of uncertainty regarding optimal practice.[2] Enhanced recovery for TJA serves as a salient example of the tension between these 2 types of variation. Major gains have been made in minimizing variation in care processes to reduce length of hospital stay and readmission after TJA. However, in parallel, significant heterogeneity and complexity in clinical content have evolved within reported protocols. Ironically, this has occurred on a background of applying standardization to the very process of creating the pathways themselves.[3]

Despite this complexity, positive outcomes after total joint arthroplasty continue to be reported. This raises a series of pragmatic questions: *Which elements are necessary*? *Which ones are sufficient*? and *How can we reconcile variation in clinical content with the goal of standardized care*? These questions are occurring in the current climate in which calls for a return to fundamental ERAS principles based on targeted modulation of procedure-specific physiology are being made.[4-5]

To address these issues, we consider recent evidence suggesting that variation within a set of core protocol elements may be less important than providing the core elements themselves within pathways for TJA. We then update the literature surrounding variation in care delivery. Finally, we highlight differences in a selection of THA and TKA pathways from a range of international practice settings, each of which are associated with favorable outcomes after TJA. We speculate that provided care is rigorously defined, delivered and assessed, variation in details of some content elements is reasonable and may be associated with successful local outcomes.

Content variation: Essential elements within care pathways for total joint arthroplasty

Over recent decades, clinical pathways and care programs for THA and TKA have undergone significant evolution as enhanced recovery has become standard of care.[6-7] A wealth of evidence has accumulated to inform clinical and society guidelines for pathway content, which in turn have been developed to guide creation and implementation of TJA protocols worldwide.[8-11] Despite these advances, society guidelines which evaluate the same or similar evidence make different recommendations for care elements, and the details of recommended elements are not always

clearly defined. These disparate recommendations present challenges not only for implementing or refining a TJA protocol, but also for directly comparing results and outcomes of published studies which include different care elements.[12-13]

There are approximately 20 clinical care elements with high quality evidence to support inclusion in a TJA pathway (Box 1).[7-10] Despite the wealth and strength of evidence, to date, there is no consensus on which care elements and combinations thereof are the most important to achieve optimal outcomes after TJA. Until such time as this is clear, attempts to develop universally accepted, fully standardized enhanced recovery pathways for TJA will be limited. Moreover, as highlighted by the differences found in guidelines and society recommendations, we may never reach a fully standardized protocol which is suitable for all TJA patients and practice settings. In lieu of this, it may be possible – indeed, preferable – to derive the essential care elements associated with optimal outcomes after TJA and leave room for variation in care based on local circumstances and patient-individualized care (until future research provides conclusive guidance for the currently undefined care elements).

In an early analysis of this question, Khan and colleagues demonstrated that an enhanced recovery protocol including a few core components was associated with reductions in complications, length of stay (LOS), and 30-day mortality.[14] The pathway featured patient education, multimodal analgesia with local anesthetic infiltration, standardized anesthesia, tranexamic acid, and early mobilization. In the most recent affirmation of these early results, the POWER2 trial concluded that optimal outcomes and the lowest incidence of complications after TJA were among patients who received regional anesthesia, tranexamic acid and early mobilization.[15] Likewise, in a US-based population analysis of enhanced recovery elements and outcomes, multimodal analgesia,

tranexamic acid, anti-emetics on the day of surgery, and early mobilization had the strongest individual effects on reducing complications and LOS.[16] A similar population-based study subsequently confirmed these results, and further concluded that the incidence of complications differed minimally with different combinations of care elements.[17]

As the preceding discussion suggests, the 3 core elements which are consistently associated with improved outcomes after TJA are: 1) tranexamic acid, 2) multimodal analgesia with locoregional techniques and 3) early mobilization and rehabilitation.[18] Despite this evidence, there is considerable variation in how these elements are integrated into TJA pathways. Further, each represents an exemplar of how variation in the mode of provision may be less important than providing the element itself.

Tranexamic Acid

Of all the antifibrinolytic medications, tranexamic acid (TXA) has been the best characterized agent for minimizing perioperative blood loss and transfusion requirements after THA and TKA.[19] Two recent network meta-analyses both concluded that all TXA formulations were statistically superior to placebo for the outcomes of blood loss and transfusion after THA or TKA.[20-21] These benefits were found irrespective of whether intravenous, topical, oral, or combined intravenous/topical TXA regimens were provided.

Despite the publication of more than two thousand studies on TXA and outcomes after TJA, there is no consensus regarding the most effective and safest route, dose and timing of administration (Figure 1). Although all routes and formulations of TXA are effective,[19-23] emerging data support oral TXA as non-inferior to the intravenous route for minimizing bleeding, transfusion and infection, without increasing the risk of deep vein thrombosis.[22-23] Of particular relevance for

value-based care, oral TXA is significantly less expensive than intravenous or topical formulations, and arguably easier for perioperative staff to access and administer.[22-23] These benefits would be expected to decrease direct and indirect costs of care (via reduced workload of perioperative personnel) and translate into cost-saving benefits for healthcare systems. Oral TXA may also represent a patient-safety advantage over intravenous formulations by eliminating inadvertent intrathecal administration, as has been described in case reports in patients undergoing spinal anesthesia for TJA.[24]

Multimodal Analgesia with Locoregional Techniques

Providing effective, opioid-sparing multimodal analgesia with 2 or more classes of analgesic agent is associated with improved outcomes after TJA. Although expert guidelines consistently recommend multimodal analgesia, the specific choice and combination of agents has historically been left to local stakeholders (Figure 2). Typically, unless precluded by patient risk factors and co-morbidities, acetaminophen, a non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor and a gabapentinoid form the basis of the analgesic regimen within TJA pathways.[8-11,25] Notably, although no new analgesic agents have been added to the formulary in recent years, considerable evidence has accumulated to support removing gabapentinoids from TJA pathways in gabapentinoid-naïve patients.[11,26-27] This is based on years of accumulating data suggesting minimal evidence of benefit for acute pain, and significant risk of harm, particularly when co-administered with opioids.[26-27] Indeed, the latest PROSPECT guidelines specifically recommend against providing gabapentinoid therapy as part of the analgesic management of THA.[11]

Peripheral nerve blocks (PNB), local infiltration analgesia and/or periarticular injection of local anesthetics have assumed a central role in pathways for THA and TKA in many centers.[28] There is evidence that both single injection and continuous catheter techniques improve analgesia, minimize opioid consumption, conserve hospital resources, and reduce cardiac, pulmonary and renal complications after TJA.[29] Currently, reports of novel blocks and regional analgesic strategies are outpacing capacity to assess the relative value and benefits when added to pathways for TJA.[30-33] Nonetheless, the majority of clinical guidelines recommend routine use of peripheral nerve blocks for TJA.[8,9,11,29] A notable exception to this is the 2019 guideline on TJA from the Enhanced Recovery After Surgery Society, which did not find compelling evidence for recommending routine use of PNB for TJA.[10] Rather, simple multimodal opioid-sparing regimens including high-dose preoperative steroid administration plus high-volume local anesthetic infiltration have been proposed as an alternative strategy.[34-35]

Early Mobilization

It is unsurprising that good analgesic control leads to early mobilization, which in turn is associated with globally improved outcomes following TJA. Early mobilization in the first 24 hours after THA or TKA is consistently effective for reducing LOS, acute early complications, thromboembolic events, morbidity, mortality, and improving patient satisfaction.[36-39] Despite widespread endorsement of early mobilization as part of enhanced recovery guidelines in many surgical subspecialities,[10,40] it has previously been reported that less than 10% of TJA patients ambulate on the day of surgery.[41] Reasons for this are speculative but have been proposed to include; patient, structural, and cultural related issues.[42] For example, the ideal time to initiate mobilization is undefined, and often left to the discretion of nurses and physical therapists.[43] Delayed mobilization may also be related to institutional practice and local protocols, where some

units encourage early mobilization, and others do not. Patient motivation is likely to be a key driver of time-to-mobilization, and a factor which is not modifiable by anesthetic or surgical technique, but which may be increased following the COVID-19 pandemic. It has been proposed that patients are likely to be strongly motivated to get home sooner following surgery to distance themselves from possible exposure to COVID-19.[44] In addition, the recent increase in the number of TJAs performed within ambulatory surgical centers, and the growing trend towards outpatient TJA surgery will further necessitate the structural and cultural changes needed to facilitate early mobilization and achievement of independent mobility so that discharge requirements are achieved on the day of surgery.

Outcome variation: Standardizing measurement of pathway efficacy

Interestingly, debates regarding the optimal selection of pathway elements have not necessarily focused on outcomes. Healthcare systems may not value pain, opioid-consumption, opioid-related side effects except in so far as they affect length of stay, and there is rarely an incentive to return TJA patients more quickly to normal function and everyday activities. Patient-focused outcomes have largely been missing from evaluations of interventions directed toward reducing LOS. Most studies evaluating pathway efficacy are restricted to traditional outcomes, such as LOS, readmission, mortality, and complications, and may not be sufficiently sensitive to detect benefits of individual clinical interventions, like peripheral nerve blocks, which would not be expected to influence mid-to-long-term outcomes.[45] More recently, studies have considered patient-reported outcome measures and system-wide cost savings as indices of pathway efficacy.[46] These have increased the complexity of effectiveness analyses, but also the relevance of study findings, and are required for comparative evaluation of published studies.

A complete review of methods to standardize outcomes assessment is out with the scope of the current manuscript, but calls have been made to derive a core set of outcomes and measurements for enhanced recovery programs. In addition to process evaluation, these should ideally reflect the different perspectives of key stakeholders (patients and practitioners) as well as the stage of recovery, and assessment of procedure-specific clinical improvement [45-46] In the case of TJA, it should also be acknowledged that although patient-reported outcome measures (PROMs) show improvement in most patients, discrepancies are seen when compared with measures of physical performance, both in the early and later recovery phase.[47-48]

Process variation: Quantifiable & unquantifiable aspects of care pathway delivery

Enhanced recovery efficacy cannot be considered in isolation from pathway adherence. Along with minimizing variation in care, strict pathway adherence has long been advocated as an effective strategy to reduce complications after surgery.[49] Ample evidence to support this concept can also be found for patients undergoing THA and TKA where adherence above a minimum threshold or minimum number of care elements within a pathway has been associated with reductions in any complication (cardiopulmonary, stroke, acute kidney injury, thromboembolic event and infection)[15-17,50] major complications (cardiopulmonary,[16,17] in-hospital mortality,[16] infection,[15] transfusion[15-17] and need for revision surgery[15]), and LOS,[15-17,50] in both clinical and population-based studies.[15-17,50]

Early data to support this concept associated lower costs of care and shorter LOS after TJA with a pathway adherence threshold of 80%.[50] Recent population-based and large clinical studies evaluating the impact of increasing the number of care components in TJA pathways have

similarly associated higher numbers of components with incremental decreases in "any complication" rates.[15-17] Interestingly, in these studies, overall adherence approximated 70%, and greater adherence to classic protocol care elements was generally associated with better outcomes, shorter LOS and reductions in mild, moderate and severe postoperative complications.[15-17,50]

Individual complications may also be more reliably minimized when a pathway is provided *en bloc* compared to delivering individual targeted interventions. A recent systematic review and meta-analysis on prevention of postoperative pulmonary complications found that the greatest protective benefits were among patients cared for under an enhanced recovery pathway, compared to those who received single or combined pulmonary or respiratory interventions.[51]

It is unclear why 'the whole is greater than the sum of the parts', but emerging data suggests this may be attributed, at least partially, to staff experiences of delivering care. This is likely to be a key aspect of successful outcomes, but one which is subject to great variability and is difficult to quantify. Nonetheless, a recent systematic review of care delivery by enhanced recovery teams concluded that evidence-based guidelines were useful for improving patient care, but outcomes mainly improved over time as staff attitudes towards enhanced recovery became more favorable and practices became progressively ingrained.[52] Further, an ethnographic study on enhanced recovery for TJA implementation found that care was viewed as a 'message' that had to be accepted and communicated consistently by staff, but ultimately, successful implementation requires empowering patients to work towards their own recovery. [53]

Real-World Examples: Variable pathways, similar outcomes after total joint arthroplasty

This discussion illustrates a current tension in selecting care elements for TJA pathways: some elements (like optimal TXA route, timing and dosing) have a wealth of options for delivery and reasonable evidence to support any of them for inclusion in a TJA pathway. Others (like peripheral nerve blocks) are associated with gaps in knowledge that preclude straightforward selection. Unquantifiable local aspects of care organization and delivery and patient factors also clearly impact outcomes but can't be directly incorporated into the pathways themselves. Each result in the requirement to make choices in the face of uncertainty. How should we decide which elements to include? Individual selection is likely to be based on practitioner experience, local resource availability, and patient population.

We propose that 1) provided the outcomes of interest are standardized, 2) the pathway includes the core elements associated with favorable outcomes and 3) optimal outcomes are achieved for the local practice setting, the individual details of the core elements provided to the patient probably matter less than ensuring care is organized and delivered according to core enhanced recovery principles. To explore this, we considered components of TKA and THA pathways from a range of international practice settings and compared measured outcomes achieved according to each pathway. This comparison is intended to be illustrative and to identify gaps in consensus and variation in chosen outcomes which assess pathway efficacy. We emphasize that Table 1 is based on details available in the published literature and may not represent the complete, up-to-date practice within the included institutions at the time of writing. This highlights the dynamic nature of care pathways, and that real-world practice will often lag (and sometimes lead) the published evidence.

We included pathways from 5 enhanced recovery centers for TJA: 1 from the United Kingdom (Healthcare NHS Foundational Trust, Northumbria), 1 from Denmark (Copenhagen University Hospital, Hvidovre), 1 from Canada (Hôpital Maisonneuve-Rosemont, Montreal) and 2 from the USA, of which one was a Veteran's Administration Hospital (VA Palo Alto Health Care System, Palo Alto, California) and one was a tertiary care academic medical center (Mayo Clinic, Rochester, Minnesota).

Of the 3 core care elements with the most evidence to support inclusion in TJA pathways, day-of-surgery mobilization was the only component with 100% agreement between the centers. Although all centers include TXA for THA and TKA, there was no consensus regarding dosing strategy, timing or route of administration, and none included oral TXA. All centers included prophylaxis against postoperative nausea and vomiting, although details of the individual agents provided, and whether given pre- or intraoperatively varied across centers. Only Copenhagen University Hospital included high dose methylprednisolone as an intraoperative agent.

There was reasonable agreement in terms of combinations of oral and iv analgesics, with all centers providing acetaminophen or paracetamol, and all including an NSAID. Celecoxib was the most commonly chosen NSAID. There was poor agreement in choice, dose and route of opioid administration, although all centers included opioids with administration parameters (usually according to pain score and with progression from weak to strong opioids). Likewise, choice, dose and duration of gabapentinoid were not uniform between the centers. Differences in each of these elements may be influenced by local regulatory and prescribing practices, as well as by different patient expectations and demands.

Although all centers included a source of loco-regional analgesia, the details of individual techniques represented a prominent source of variation. Some centers restricted local anesthetic

delivery to surgeon-administered periarticular injection, while others included anesthesiologist-administered fascial plane blocks, continuous catheter techniques, and combinations of blocks and injections. Given that each center published compelling data to support their choice(s) of locoregional technique, variation in the details between centers is likely to reflect, at least in part, differences in institutional expertise and culture. These aspects are likely to be crucial to overall pathway success at the local level, but may not be generalizable to other geographic and practice settings.

Choice of outcomes was likewise variable, with most centers reporting their experiences with traditional enhanced recovery outcomes and when evaluating the pathways as a whole: LOS, complications, readmission and resource consumption. In contrast, patient-relevant outcomes, like pain and satisfaction were more frequently found when studies focused on optimizing individual care elements within a defined pathway. Despite these points of variation, the global effect of pathways was similar with consistent results found for standard enhanced recovery outcomes.

Future Directions

One of the major successes of enhanced recovery has been to translate large variations in care into standardized practice. However, it has become evident that no two pathways for THA or TKA are the same. According to fundamental enhanced recovery principles, this would be considered a shortcoming. Conversely, as presented here, evidence suggests that optimal outcomes can be achieved by allowing some variation in detail, provided the core elements of care are delivered. Effective pathways rely on translating best evidence into practice, yet they also require individual tailoring according to local experience and resources. Likewise, greater adherence to enhanced recovery elements improves outcomes, but what are the proper elements to which we should adhere? Evidence continues to support TJA pathways which include blood management,

multimodal analgesia and early mobilization as the basis of the care trajectory. Consequently, the emphasis should be on providing these essential elements of care, rather than on perfecting the details thereof. In this sense, adaptation of enhanced recovery care to local culture becomes more important than defining all details of each care element. For example, providing opioid-sparing analgesia via locoregional techniques assumes more global importance than the individual peripheral nerve or field block selected for the pathway. On the other hand, minimizing variation *within* the institution may be more important than seeking to create a single pathway suitable for all settings and patients. To this end, pathways should be kept simple (including the fewest number of active and proven care elements) so that they are reproducible, and all care elements can be delivered as intended to every patient (and monitored via local compliance audit).

Now that enhanced recovery for TJA has largely been integrated into healthcare systems worldwide, the future task for anesthesia and enhanced recovery care teams is to achieve the 'pain and risk-free' procedure. Adding to the challenge, this will need to be achieved in conjunction with rising patient demand and medical complexity. Logically, as patient-specific risks are evaluated and incorporated into care pathways, further variation and individualization of care may be expected. Indeed, as care and outcomes continue to improve, TJA is increasingly being offered to patients who were formerly considered to be poor surgical candidates. Key demographics for optimization and risk reduction include the patient with diabetes mellitus, obesity, advanced age, frailty and/or cognitive dysfunction. At the other end of the spectrum, shifts in practice patterns and reimbursement mandate more TJA procedures will be performed in the ambulatory setting and on a same-day discharge basis. A balance between standardization and permissive variation are likely to be key to successful translation of TJA from hospital to ambulatory settings and to the future of enhanced recovery for THA and TKA.

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Box 1
Standard care elements for total joint arthroplasty pathways

Preoperative
- Patient education and expectation-setting
- Optimization of modifiable risk factors (detect and correct anemia, smoking cessation, nutritional support, cardiopulmonary and physical optimization where indicated)
- Avoid prolonged fasting
- Pre-emptive analgesia (Figure 2)

Intraoperative
- Short-acting anesthetics (neuraxial or TIVA-based general anesthetic)
- Multimodal analgesia (local infiltration analgesia, peripheral nerve blocks and continuous catheters; neuraxial and intrathecal analgesia; maximize use of non-opioid intravenous agents)
- Goal: euvolemia
- Goal: normothermia
- Timely antibiotic administration
- Timely antifibrinolytic administration (Figure 1)
- PONV prophylaxis

Postoperative
- Continue non-opioid-based multimodal analgesia
- Early mobilization
- Early intravenous / arterial line removal
- Early oral nutrition
- Bowel regimen
- Delirium prevention: screening and early intervention

Enhanced recovery pathways for total joint arthroplasty comprise evidence-based, multidisciplinary, multimodal components of care.[7-11]

Abbreviations: TIVA total intravenous anesthesia; PONV post-operative nausea and vomiting.

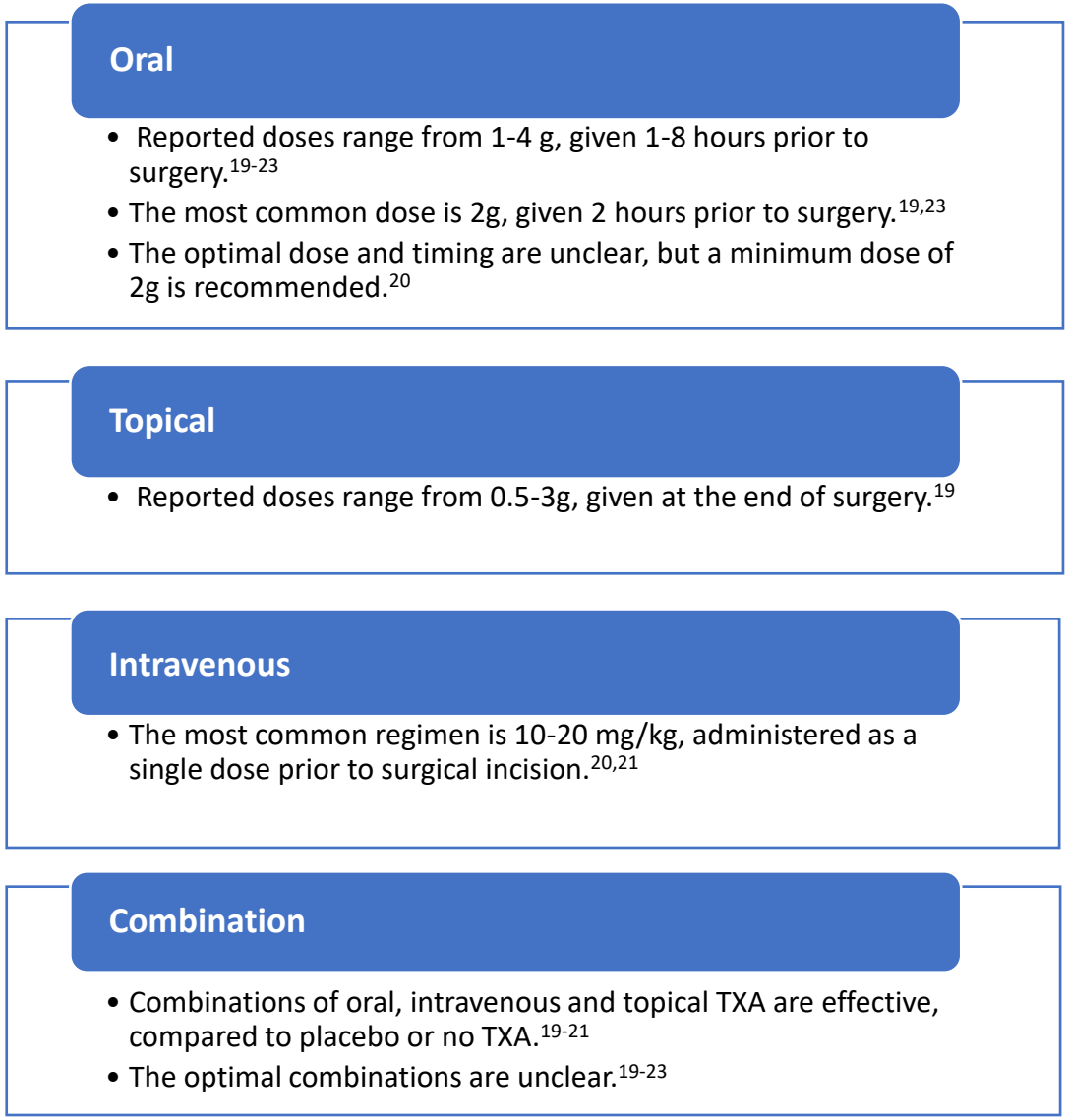

Figure 1: Tranexamic acid options for total joint arthroplasty pathways.

Controversy persists regarding the optimal regimen and formulation of TXA to protect against blood loss and transfusion. There is consensus that TXA should be included in THA and TKA pathways, where not contraindicated.[8-10, 19-23] Irrespective of route and formulation, higher doses and multiple doses are not recommended.[19-21]

Abbreviations: THA total hip arthroplasty; TKA total knee arthroplasty; TXA tranexamic acid.

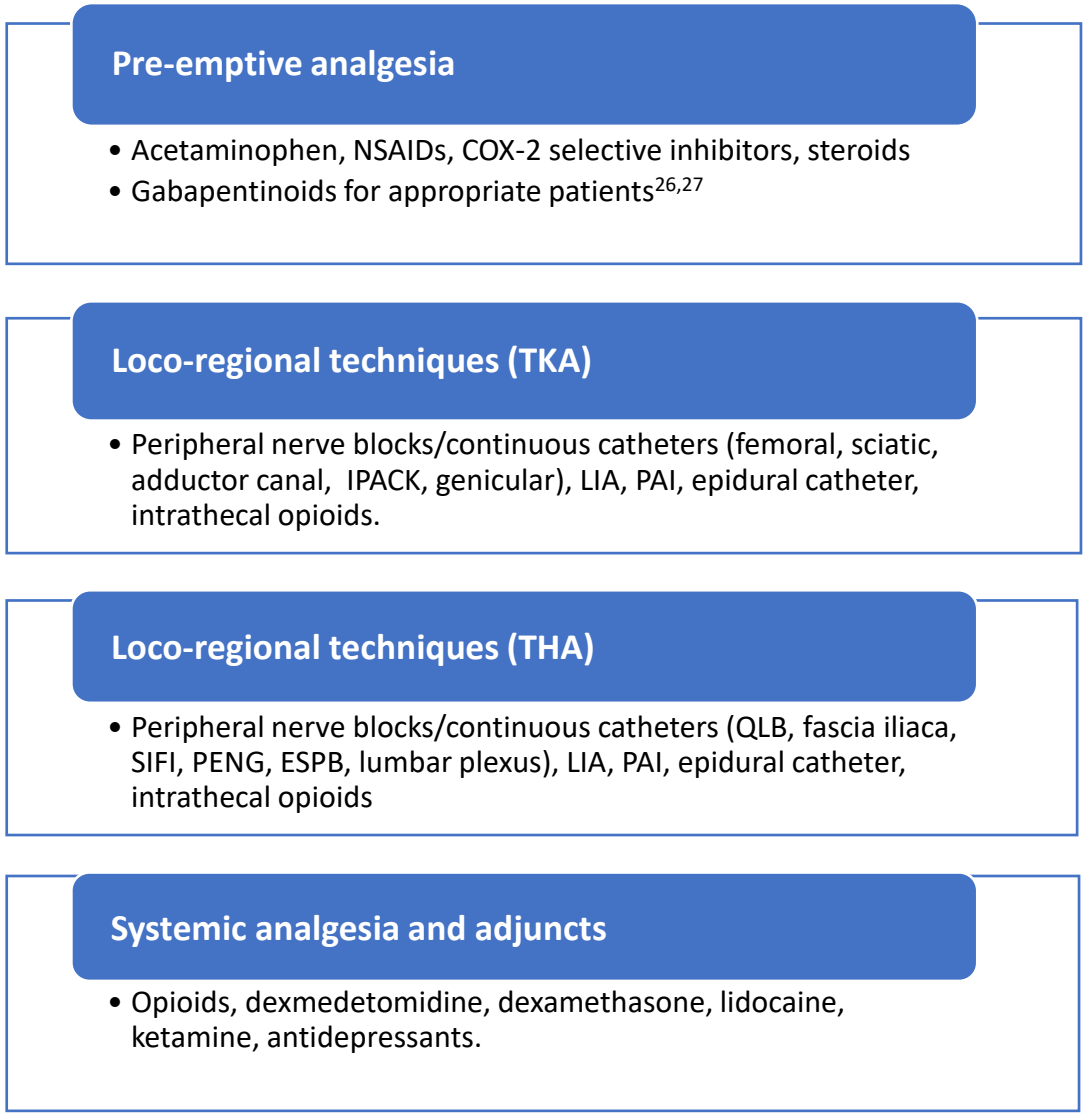

Figure 2: Analgesic options for total joint arthroplasty pathways. Controversy persists regarding the optimal analgesic regimen. There is consensus that opioid-sparing multimodal analgesia should be included in THA and TKA pathways. A reasonable strategy includes combinations of non-opioid agents, loco-regional techniques and opioids as needed (at the lowest dose / shortest duration required).[8-10]

Abbreviations: COX cyclo-oxygenase; ESPB erector spinae plane block; IPACK interspace between the popliteal artery and posterior capsule of the knee; LIA local infiltration analgesia; NSAID non-steroidal anti-inflammatory; PAI periarticular injection; PENG pericapsular nerve group; QLB quadratus lumborum block; SIFI suprainguinal fascia iliaca ; THA total hip arthroplasty; TKA total knee arthroplasty.