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Regional and Multimodal Analgesia to Reduce Opioid Use After Total Joint Arthroplasty: A Narrative Review

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Abstract *Background:* Elective total joint arthroplasty may be a gateway to long-term opioid use. *Questions/Purpose:* We sought to review the literature on multimodal and regional analgesia as a strategy to minimize perioperative opioid use and control pain in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). *Methods:* We conducted a narrative review to assess the state of the evidence informing opioid-sparing analgesics for THA and TKA. A PubMed search was conducted for English-language articles published before April 2018. We preferentially included well-designed randomized controlled trials, systematic reviews, and meta-analyses. Where the highest levels of evidence were not yet apparent, we evaluated retrospective and/or observational studies. *Results:* Multimodal analgesia emphasizing nonsteroidal anti-inflammatory agents and acetaminophen is associated with decreases in perioperative opioid use for THA and TKA. Regional analgesia, including peripheral nerve blocks and local infiltration analgesia, is also associated with decreased perioperative opioid use for THA and TKA. Emerging topics in postarthroplasty analgesia include (1) the value of nonsteroidal anti-inflammatory drugs, (2) the use of peripheral nerve catheters and extended-release local anesthetics to prolong the duration of opioid-free analgesia, and (3) novel peripheral nerve blocks, exemplified by the IPACK (interspace between the popliteal artery and posterior capsule of the knee) block for TKA. *Conclusions:* The use of multimodal analgesia with regional techniques may decrease perioperative opioid use for patients undergoing THA and TKA. These techniques should be part of a comprehensive perioperative plan to promote adequate analgesia while minimizing overall opioid exposure.

Keywords opioid crisis · orthopedic surgery · total joint arthroplasty · multimodal analgesia · regional analgesia · peripheral nerve block

Level of Evidence: Level III

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Introduction

Surgery is a potential risk factor for new long-term opioid use. A recent database study comparing opioid-naïve US adults undergoing surgery to a nonoperative control cohort found a significantly higher incidence of new persistent opioid use in surgical patients (approximately 6%) than in nonsurgical patients (0.4%) [8]. Orthopedic surgery, including total joint arthroplasty (TJA), has been particularly associated with long-term opioid use and misuse [88]. The rising demand for total hip arthroplasty (THA) and total knee arthroplasty (TKA) mandates strategies to minimize opioid exposure and protect patients from long-term opioid dependence [65].

It follows that decreasing perioperative opioid exposure may contribute to a decrease in postdischarge opioid use. Multimodal nonopioid analgesia has recently been shown to decrease postoperative opioid prescribing by over 18.5% after elective THA and TKA [73]. Elements of a multimodal analgesia regimen for TJA typically include the use of regional techniques (peripheral nerve blocks, catheters, and local infiltration analgesia) combined with systemic

analgesics (acetaminophen, ketamine, and nonsteroidal anti-inflammatory drugs [NSAIDs]) [89]. Each has been shown to independently decrease perioperative opioid consumption, while facilitating analgesia after a variety of surgical procedures [51]. We reviewed the evidence on multimodal and regional analgesia in decreasing perioperative opioid use for elective TJA.

Methods

We conducted a review of the literature to examine the latest evidence on the following question: Which nonopioid analgesics provide adequate pain control while minimizing opioid consumption after THA or TKA? Literature reviews for each individual analgesic were performed in PubMed for English-language articles published before April 2018. Each search initially targeted THA and TKA. If no THA- or TKA-specific literature was identified, the search was broadened to surgical procedures in general and the relevant articles extracted. Given the volume of literature in this field, a hierarchical method of inclusion was employed based on study design. If we identified a well-designed systematic review (SR) or meta-analysis (MA), the study was included. Where the highest levels of evidence were lacking, we included randomized controlled trials (RCTs), observational studies, or cohort studies. Results are described narratively.

Results

Systemic Multimodal Analgesia

The concurrent use of nonopioid systemic analgesics may provide additive or synergistic effects on pain control while minimizing opioid use and opioid-related adverse effects. Commonly studied classes of nonopioid systemic analgesics include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), N-methyl-D-aspartate (NMDA) receptor antagonists, and gabapentinoids.

Nonsteroidal Anti-inflammatory Drugs

TKA There are two RCTs [80, 83], one observational trial [43], and one MA [58] examining the use of oral (PO) and intravenous (IV) NSAIDs (including cyclooxygenase-2 [COX-2] inhibitors) for the treatment of pain after TKA. Results indicate that the use of NSAIDs is associated with a reduction in pain scores and a significant opioid-sparing effect—a benefit that was confirmed for opioid-naïve and opioid-tolerant patients [43].

THA There are no large-scale RCTs or SRs of the analgesic efficacy of preoperative NSAIDs in THA surgical patients. There is one SR examining the use of NSAIDs for postoperative pain after THA, which associated NSAIDs with significantly lower pain scores and opioid requirements [34].

NSAIDs have an analgesic ceiling and may be associated with platelet dysfunction, gastrointestinal irritation/bleeding, and renal dysfunction. Despite these concerns, an MA of 27 RCTs involving a variety of surgical procedures [26] and a postmarketing study of ketorolac [94] indicate that NSAIDs are not associated with an increase in postoperative bleeding.

Acetaminophen

TKA There are two retrospective observational studies of IV acetaminophen in TKA. Neither study found an analgesic benefit nor any reduction in perioperative opioid use [44, 75]. There is one RCT comparing PO and IV acetaminophen to placebo in patients receiving comprehensive multimodal analgesia and spinal anesthesia [76]. There were no additional analgesics or opioid-sparing benefits of acetaminophen.

THA One study examined a single dose of postoperative IV acetaminophen in patients undergoing THA [86]. It significantly reduced pain scores and opioid consumption.

Combined THA/TKA Studies There are three SR/MAs of PO and/or IV acetaminophen analyzed in combined THA and TKA cohorts [7, 95, 107]. When added to multimodal analgesia, IV acetaminophen reduced pain and opioid consumption after TJA [107] and when compared to placebo [57]. One SR/MA comparing PO to IV acetaminophen failed to find any difference between route of administration and pain scores or opioid consumption [95].

Gabapentinoids

TKA Two MAs associate perioperative gabapentinoids with a decrease in opioid consumption after TKA [18, 31]. However, the analgesic benefits described are inconsistent, with one MA concluding no decrease in pain with ambulation or improvement of knee flexion in patients receiving gabapentinoids [31] and the other concluding analgesic benefits [18]. A minority of the numerous RCTs/observational trials studying gabapentinoids in TKA demonstrated a decrease in postoperative pain [52, 74]. When added to a comprehensive multimodal analgesic regimen, a recent RCT concluded, gabapentin provided no additional analgesic benefits [105].

THA There are four RCTs [12, 13, 78, 110] and two MAs [32, 64] of perioperative gabapentin for THA. Three RCTs [13, 78, 110] failed to show a decrease in perioperative opioid consumption with gabapentinoids. The MAs suggested an opioid-sparing capacity for gabapentinoids, but the analgesic benefit was inconsistent. In one RCT, when gabapentin was added to a comprehensive multimodal analgesic regimen, no clinically important reductions in postoperative morphine consumption, pain scores, opioid-

related side effects, or functional improvements were found [78].

Other Analgesic Agents

N-Methyl-D-Aspartate Receptor Antagonists

NMDA receptors have been implicated in nociceptive processing. Clinically available NMDA receptor antagonists include ketamine, magnesium, and dextromethorphan.

Ketamine

TKA There are three RCTs/observational trials examining IV ketamine in TKA [2, 5, 79]. Taken together, results suggest that addition of low-dose (sub-anesthetic) IV ketamine may decrease postoperative pain, decrease opioid consumption, and improve mobilization after TKA.

THA There is one RCT examining the role of ketamine in THA [81]. Use of ketamine significantly decreased opioid consumption at 24-h post-surgery, facilitated rehabilitation at 1 month, and decreased postoperative chronic pain up to 6 months after THA.

Magnesium and Dextromethorphan

There are no studies specifically examining either of these agents in TKA/THA. However, data from MAs in primarily nonorthopedic patients suggest that use of IV magnesium infusion in the perioperative period [14] or oral dextromethorphan [47] are independently associated with a decrease in postoperative pain and opioid consumption.

Lidocaine

TKA There are no studies specifically examining the use of IV lidocaine in patients undergoing TKA.

THA There is one RCT examining the use of IV lidocaine in patients undergoing THA [67]. Compared to saline, IV lidocaine (1.5 mg/kg bolus, followed by 1.5 mg/kg/h infusion) did not offer analgesic benefits on postoperative pain scores.

Non-TKA/THA There are three MAs [46, 48, 100] examining perioperative IV lidocaine infusions in nonorthopedic surgical procedures. Taken together, results suggest that perioperative IV lidocaine infusions may be associated with decreased postoperative pain, reduced opioid consumption, and earlier return of gastrointestinal function.

Regional Analgesia

Use of local-anesthetic-based techniques may provide mid-to-long-duration opioid-free analgesia. Commonly studied regional analgesic methods include peripheral nerve blocks, catheters, extended-duration local anesthetics, and surgeon-administered local infiltration analgesia.

Epidural Analgesia

Compared to systemic opioid analgesia, epidural analgesia is associated with superior pain control, an opioid-sparing benefit, and fewer opioid-related adverse effects after THR and TKA, two MAs show [7, 101]. These benefits appear to extend well into the postoperative period but disappear by 18 to 24 h after surgery.

A recent SR confirmed the findings from these MAs but highlighted several liabilities of epidural analgesia [11]. Important side effects of epidural analgesia include higher risk of motor/sensory block, delayed ambulation, urinary retention, and hypotension. Additional concerns include how to manage anticoagulation in the setting of an epidural catheter, and how practice settings lacking comprehensive regional anesthesia services can safely and effectively manage an epidural program [35].

Peripheral Nerve Blocks

In recent years, there has been a shift toward the use of peripheral nerve blocks (PNB) and peripheral nerve catheters (PNCs) to control pain while avoiding some liabilities of epidural analgesia.

TKA Distributions of the femoral and sciatic nerves are targeted for PNB after TKA. Two MAs compare PNB to epidural analgesia after TKA [22, 25]. The literature additionally includes 20 MAs [1, 3, 17, 21, 24, 27, 36, 40, 50, 54–56, 60, 61, 70, 77, 98, 99, 109, 112], three SRs [4, 10, 104], and three large-scale observational studies [23, 69, 72] of combinations of PNBs and local-anesthetic infiltration techniques for analgesia and opioid-sparing capacity after TKA. Compared to placebo (or no-block), all PNBs studied provide superior analgesia and reduce IV patient-controlled analgesia (PCA), opioid consumption, and opioid-related adverse effects [1, 10, 27, 77, 104]. Importantly, the analgesia provided by PNBs appears to be comparable to epidural techniques but without the adverse effects and pragmatic pitfalls described above [11, 22, 25].

Classically, femoral nerve block (FNB) has been performed for post-TKA analgesia. An early SR on the relative benefits compared FNB to any other analgesic technique [10]. FNB was superior to opioid-containing IV PCA and equivalent to epidural for post-TKA analgesia, opioid consumption, and nausea/vomiting. The main drawback to FNB is motor weakness and concomitant increased risk of falls [71].

The adductor canal block (ACB) may offer motor nerve-sparing benefits and has been studied as an alternative to FNB in this regard. Nine MAs compare FNB to ACB for

analgesia and fall risk after TKA [17, 24, 36, 40, 50, 55, 56, 99, 112]. Overall, the results suggest that ACB offers at least equivalent analgesia, but with superior ambulation potential, less quadriceps weakness, and faster recovery after TKA than FNB.

According to the conclusions of two SR/MAs [27, 61] and one MA [1], adding a sciatic nerve block to FNB [1, 27] or local infiltration analgesia [61] (vs. either alone) provides additional analgesia and further reduces postoperative opioid consumption after TKA. However, the body of evidence for sciatic nerve block has been described as overall low quality [87]. Given that sciatic nerve block can delay physical therapy and ambulation after TKA, well-designed prospective RCTs on the risks and benefits of sciatic nerve block are needed [61].

An alternative approach to target posterior knee pain after TKA has recently been described. The interspace between the popliteal artery and posterior capsule of the knee (IPACK) block delivers local anesthetic to the posterior aspect of the knee, providing analgesia while preserving motor strength [19]. One retrospective study [97] and one prospective cohort trial [82] evaluate the role of IPACK for TKA. Results for analgesia and opioid consumption were mixed, with one study suggesting improved pain scores (but no effect on opioid consumption) [82], and the other suggesting reduced opioid consumption, but no effect on pain scores [97]. However, both studies concluded IPACK plus ACB optimized physical therapy outcomes and shortened length of hospital stay.

Peripheral Nerve Catheters

The preceding discussion highlights effective analgesia strategies in the immediate postoperative period. However, there is significant unmet clinical need to provide ongoing analgesia beyond the duration of epidural/PNBs. Accordingly, research into methods for extending the duration of PNBs has focused on the role of PNCs.

There are two narrative reviews on the use of PNCs for analgesia for a range of indications, including TKA/THA [38, 39]. The updated review included six RCTs exploring the use of adductor canal PNC after TKA [39]. Evidence was mixed for analgesia, ambulation, and opioid consumption. The author called for research into the role and utility of PNC for TKR as a priority. An accompanying editorial suggested the state of the evidence was limited to recommend PNCs routinely for TJA; although there is much benefit suggested by PNC programs, unresolved questions requiring further research include how to determine the optimal composition, duration, and value of PNC, given the resource-intense requirements [90]. Since that time, one RCT has compared ACB with adjuvant to PNC in TKA [53]. Pain scores were noninferior in the ACB group, and there were no differences in opioid consumption up to 48-h post-TKA. The authors concluded that single-shot ACB with adjuvants to extend duration may represent the more viable option for fast-track discharge after TKA.

THA For THA, options for PNBs and PNCs include psoas compartment/lumbar plexus block, fascia iliaca block, and sciatic nerve block [63].

We identified one MA [34] and five additional RCTs [37, 66, 84, 93, 106] examining the use of lumbar plexus block/catheters for post-THA analgesia. Taken together, the data indicates that the use of a lumbar plexus block/catheter is associated with significant reductions in postoperative pain scores and opioid consumption. The optimal choices of local anesthetic, dose, and duration for lumbar plexus block/catheters for THA are currently unknown. The risk of falls caused by lumbar plexus block is also uncertain but should be considered in high-risk patients [42].

One MA compares FNB to fascia iliaca block for pain scores and opioid consumption after THA and TKA [103]. No differences were seen in either outcome, or in opioid-related side effects. The authors urge caution in interpretation of the underlying studies (described as at significant risk of bias) and calling for more high-quality large RCTs with longer follow-up intervals.

Local Infiltration Analgesia/Periarticular Analgesia

Intraoperative infiltration of local anesthetics into the surgical field or around the joint space is a technique performed by surgeons for postarthroplasty analgesia.

TKA One SR [4] and seven MAs [3, 21, 56, 60, 70, 98, 109] suggest local infiltration analgesia (LIA)/periarticular analgesia (PAI) offers equivalent analgesia to PNBs or epidurals at rest, but inferior analgesia with movement. Opioid consumption and related side effects appear to be similar between the techniques. These results need to be interpreted with caution, however, because of significant methodological issues in the majority of the included studies [4, 87].

THA There are four SRs [34, 41, 68, 108], two RCTs [33, 92], and two observational studies [6, 45] examining the use and value of LIA/PAI for THA. Four additional RCTs [9, 15, 59, 91] were incorporated into the SRs referenced above [34, 41, 68, 108]. Taken together, the preponderance of data suggests that LIA/PAI reduces postoperative pain scores and opioid consumption and minimizes opioid-related adverse effects when compared to placebo or no LIA/PAI. It is unknown how LIA/PAI may add benefit to comprehensive multimodal analgesia regimens. Additionally, the optimal composition (including choice of local anesthetic and adjuvants), dose, location, and method of injection are currently unclear.

Continuous-Release Local Anesthetics

Continuous-release local anesthetics are increasingly being trialed for postarthroplasty analgesia. Liposomal bupivacaine (LB) is a novel formulation which provides slow-release bupivacaine (up to 72 h). LB is approved by the US Food and Drug Administration for LIA. There are

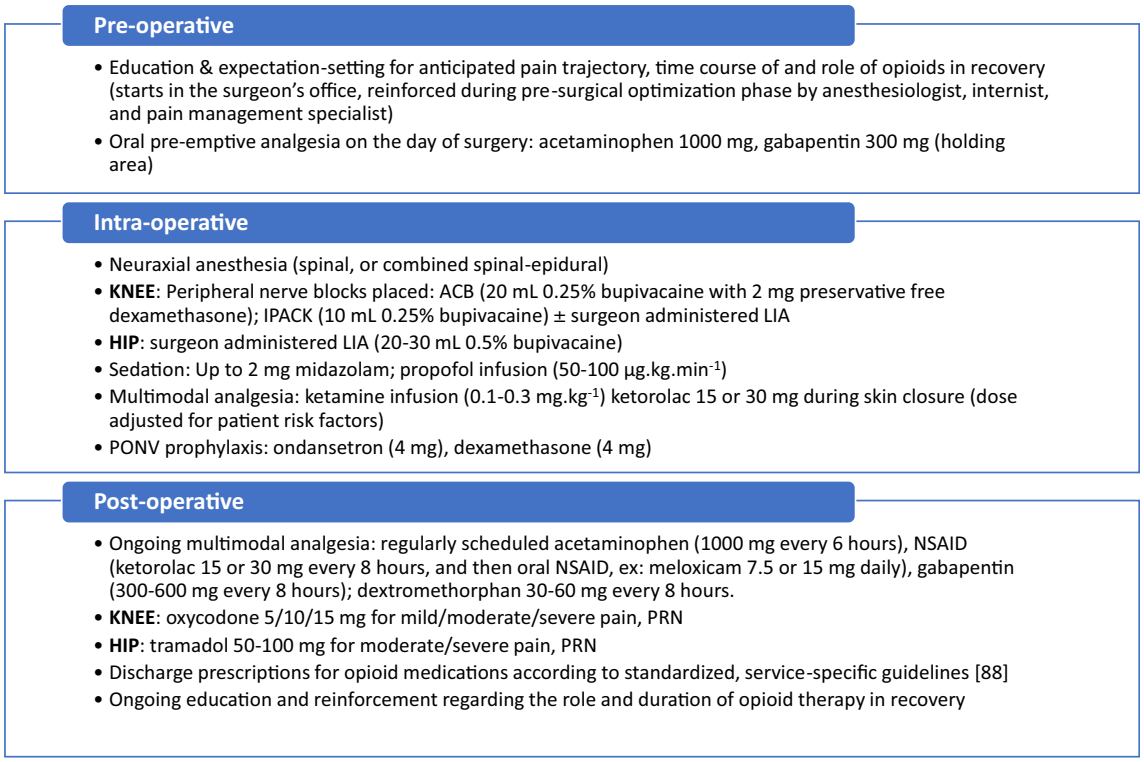

Fig. 1. An opioid-sparing approach to total joint arthroplasty. Multimodal, nonopioid analgesics form the basis of the protocol. Note that opioids are not introduced until the postoperative phase, and then only after other nonopioid analgesics have been maximized, and sufficient analgesia has not been achieved. All eligible patients should receive regularly scheduled acetaminophen and NSAID; continue gabapentin as tolerated; add dextromethorphan as tolerated, while monitoring for adequate analgesia and side effects. *ACB* adductor canal block, *IPACK* interspace between the popliteal artery and posterior capsule of the knee, *LIA* local infiltration analgesia, *PRN* as needed, *PONV* postoperative nausea and vomiting.

contradictory data regarding the analgesic benefits of LB for joint arthroplasty: a Cochrane review showed LB is associated with superior analgesia and significant opioid reduction compared to placebo (in mixed surgical subtypes but including TJA) [30]. However, when compared to plain bupivacaine hydrochloride, there were no benefits in pain scores, opioid consumption, or length of hospital stay.

TKA Three MAs compare LB to placebo- or local-anesthetic-based PAI [49, 85, 102]. One failed to conclude a clear clinical advantage [85] and the other showed no benefit of LB for pain and functional outcomes after TKA [49]. In contrast, the third associated LB with superior analgesia and opioid-sparing benefits after TKA, when compared to placebo [102]. Several methodologic issues combine to confer a very high risk of bias, including low overall volume and quality of the included studies and conflict of interest concerns regarding sponsorship of studies [30].

Although not currently approved for use in PNBs, there is one RCT comparing FNB with LB versus placebo for post-TKA analgesia and opioid use [28]. LB provided superior analgesia and minimized opioid consumption up to 48 h after surgery.

THA Two MAs compare LB to plain bupivacaine-PAI for THA [62, 111]. In both, LB significantly reduces pain scores and opioid consumption up to 48 h after THA. In addition, there was a significantly decreased incidence of nausea and vomiting in patients receiving LB. The overall quality of evidence was rated as low or very low, suggesting further well-designed trials are needed, and are likely to alter confidence in the effect. Additionally, all the included studies were small and retrospective in design.

Discussion

Elective TJA may be an entry to prolonged postdischarge opioid use. Our review suggests that multimodal analgesia with regional techniques may be opioid-sparing and instrumental in decreasing perioperative opioid use in patients undergoing TJA. These techniques should be used as part of a comprehensive perioperative plan to decrease overall opioid use while providing adequate analgesia (Fig. 1).

Multimodal analgesia forms the cornerstone of post-TJA pain management, and continuation of multimodal IV agents is recommended until the patient is tolerating an oral diet. Effective analgesic choices for post-TJA pain management include NSAIDs and acetaminophen, administered on a scheduled basis, unless there are contraindications.

The use of gabapentinoids may decrease opioid consumption, but our review suggests that the analgesic efficacy for TJA is

uncertain, and several publications question the overall analgesic benefits and safety of gabapentinoids [16, 20]. Gabapentinoids are associated with several adverse effects (sedation, dizziness, peripheral edema) and should be used with caution in elderly patients and those with renal dysfunction. Conversely, a recent double-blind placebo-controlled RCT demonstrated that gabapentin promoted earlier cessation of opioid therapy after surgery—including patients undergoing THA and TKA [29].

Other nonopioid analgesic agents may be useful for postoperative pain management for TJA, although there is relatively less data for these agents, including consensus regarding the precise dose and timing of administration. IV ketamine may be a particularly promising agent in opioid-tolerant patients. Less data is available for IV magnesium, PO dextromethorphan, and IV lidocaine in TJA. Nonetheless, data in nonorthopedic patients suggests that these agents may decrease postoperative pain and opioid consumption.

The current evidence base likewise supports the use of regional analgesic techniques to minimize opioid consumption after TJA. Recent years have witnessed a shift from epidural analgesia toward PNBs as the preference for balancing analgesic with adverse effects and minimizing systemic opioid requirements. Our review highlights the multiple options available for local anesthetic-based blocks, each of which achieves dual goals of maximizing analgesia and minimizing opioid use. However, the optimal combinations of PNBs and systemic analgesics are unknown. Recent evidence suggests that a combination of PNBs likely facilitates optimal balance after TKA [96], but data is lacking for THA. Novel PNBs (such as the IPACK block) offer additional targets to minimize postoperative pain, but more research is needed on efficacy. In addition, choices for individual regional modalities must take into account local expertise and resources, recognizing that not all institutions benefit from developed regional anesthesiology services. Here, the role of surgeon-administered LIA/PAI is likely to be particularly valuable.

Finally, the optimal duration of post-TJA analgesia is unclear—as are the methods required to achieve prolonged analgesia. Current and future research should focus on the role of PNCs to extend the duration of opioid-free analgesia, as well as more comparative studies of adjuvants to single-shot PNBs and PNCs.

In summary, effective strategies to minimize opioid consumption in patients undergoing TJA focus on nonopioid multimodal analgesia, including systemic and local-anesthetic-based techniques. Based on the literature presented here, acetaminophen, NSAIDs, and peripheral nerve blocks are especially valuable and are recommended by the authors. NMDA-receptor antagonists may help minimize opioid consumption in patients who have or are at risk of developing chronic pain. Future research is needed to determine the relative benefits of gabapentinoids, PNCs, extended-duration local anesthetics, and novel PNBs for protecting patients at risk for long-term opioid use after TJA.

Compliance with Ethical Standards

Conflict of Interest: Ellen M. Soffin, MD, PhD, and Christopher L. Wu, MD, declare that they have no conflicts of interest.

Human/Animal Rights: N/A

Informed Consent: N/A

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