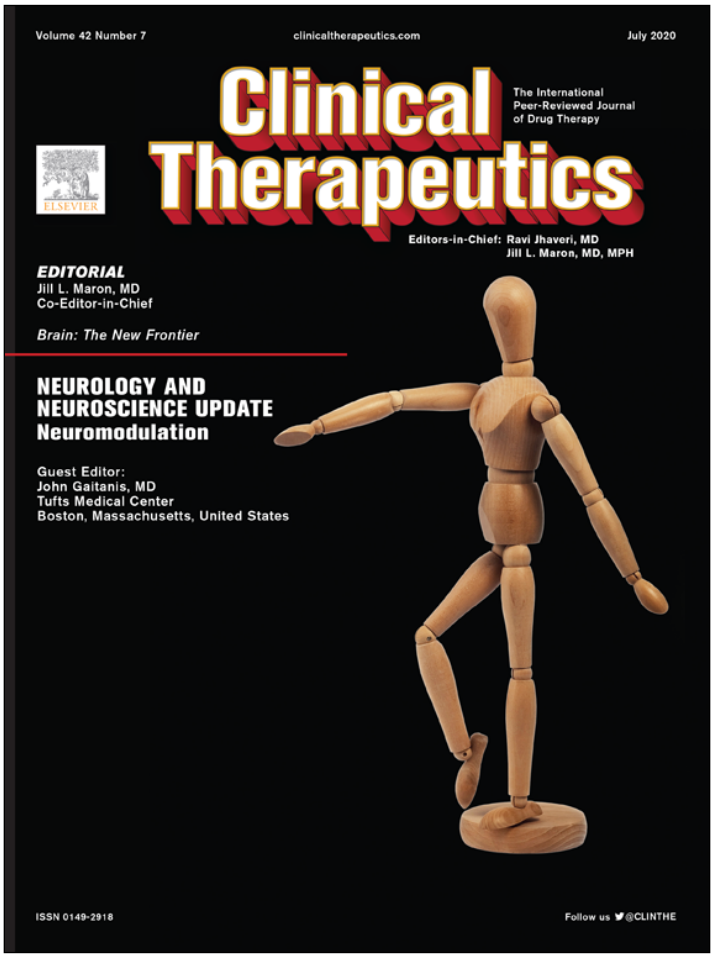

Narrative Summary of Recently Published Literature on Intravenous Ibuprofen

Stephen R. Southworth, MD, MS, MBA, FACS[1]; and
Jill A. Sellers, BSPharm, PharmD[2]

[1]Orthopaedic Institute of North Mississippi, Tupelo, MS, USA; and [2]Medavera LLC, Springfield, MO, USA

ABSTRACT

Purpose: This is a narrative review of the published literature on IV ibuprofen (IVIB) as one of the drugs used in multimodal pain management in inpatients and outpatients pre- and postoperatively and for nonsurgical pain or fever.

Methods: The efficacy, concurrent opioid use, pharmacokinetic properties, tolerability, stress response, and postoperative recovery with IVIB, which were investigated in 9 clinical studies, are presented in this narrative review. In total, 1062 adult patients and healthy volunteers were included in these 9 studies; 757 of these subjects received IVIB, and the remaining 305 received either placebo or a comparator medication.

Findings: The plasma ibuprofen level with IVIB was twice that with oral ibuprofen, and patients experienced less postoperative pain, decreased opioid use, improved quality of recovery, and reduced postsurgical fatigue and surgical stress response, and used less over-the-counter medication.

Implications: Overall, preemptive IVIB should be considered in the analgesic regimen for the management of pre- and postoperative pain, as it has a favorable safety profile, with fewer associated adverse events and serious adverse events, significantly lower levels of perioperative cytokines and catecholamines, and improved peri- and postoperative pain control with a decreased use of opioid medications. (*Clin Ther*. 2020;42:1210–1221)

Key words: fever, multimodal pain management, NSAID, perioperative analgesia, postoperative analgesia, surgical pain.

INTRODUCTION

Opioids are well tolerated and inexpensive when used appropriately; however, dependence, misuse, and diversion of opioids have resulted in a tsunami of overdose-related deaths in the United States.[1] While accounting for only 5% of the world's population, the United States accounts for 80% of oxycodone use and 99% of hydrocodone use.[2] Opioid overdose–related deaths exceed traffic collision–related deaths in the United States.[3]

In 2001, the Joint Commission introduced mandatory pain assessments in clinical settings, citing the Department of Veterans Affairs and the American Pain Society.[3] Pain became a "vital sign." While physicians' treatment of pain is an appropriate measure for patients' comfort, the trend has, unfortunately, been paralleled by a sharp increase in opioid-related toxicity and deaths.[4,5]

De-emphasis of opioid use in the pre- and postoperative timeframes has resulted in an increase in nonopioid methodologies while improving patients' subjective experience, a concept known as *enhanced recovery after surgery*. While the concept indicates a postoperative experience, it actually begins prior to surgery and is equally applicable to nonsurgical pain-reduction techniques, as well.[6] A significant proportion of postinjury and postsurgical pain is inflammatory in nature; therefore, employing nonopioid antiinflammatory techniques is a prudent strategy for reducing opioid reliance while not sacrificing efficacy in combatting pain in the clinical setting.

Accepted for publication May 2, 2020
https://doi.org/10.1016/j.clinthera.2020.05.004
0149-2918/$ - see front matter

There are classic, well-known opioid-related adverse events (AEs; eg, constipation, tolerance, dependence, drug interactions, hyperalgesia) that affect recovery and rehabilitation, which is a reason for decreasing the amount of opioids introduced into patients' medication regimens. While NSAID use also has been related to AEs (eg, gastrointestinal [GI]), the risks for tolerance, dependence, hyperalgesia, and drug interactions are lower. Utilizing less opioids and more NSAIDs, alone or in combination with opioids, can reduce the prevalence of the AEs related to opioid use.

IV ibuprofen* was approved by the US Food and Drug Administration in 2009 for the management of mild to moderate pain, moderate to severe pain in conjunction with the use of opioids, and the reduction of fever in adults; in 2015, the indications were extended to "pediatric patients 6 months and older."[7] IVIB is a nonopioid IV NSAID that manages pain signals at the nociceptors, dorsal horn, and across the blood–brain barrier.[8] Two other IV NSAIDs—ketorolac tromethamine and diclofenac sodium—are currently available in the United States for the treatment of pain, but IVIB is the only IV NSAID approved for the treatment of both pain and fever.[7] The tolerability and efficacy of IVIB have been thoroughly investigated, and 10 clinical studies have been published.[9–18] In an integrated tolerability analysis derived from all published and unpublished data on IVIB through 2015, Southworth et al[8] validated that IVIB can be given pre- and postoperatively as a well-tolerated, fundamental component of a multimodal pain-management plan and in the treatment of fever in hospitalized patients, with no time limits for duration of use.

Previously published studies have corroborated the evidence that IVIB not only is effective in pain management but also has a preferable safety profile versus ketorolac with regard to GI complications, and versus diclofenac with regard to cardiovascular complications.[19] Two meta-analyses have reviewed data on the relative risk for GI and cardiovascular complications and found that ibuprofen has a more favorable risk profile compared with both diclofenac and ketorolac regarding GI AEs and the risk ratio for cardiovascular AEs.[20,21] Concerning is that GI toxicity with ketorolac is about 5-fold that of other NSAIDs.[22]

This review continues the integrated descriptive tolerability analysis of Southworth et al[8] and presents an analysis of 9 additional previously published clinical studies of IVIB with regard to efficacy, concurrent opioid use, tolerability, pharmacokinetic properties, stress response, and postoperative recovery. In the Table 1, the studies in this updated analysis are outlined by the numbers of subjects enrolled, design, treatment/intervention, infusion time of IVIB (if applicable), initiation of IVIB dosing, and brief description of objectives). Since the initial report of the tolerability and efficacy of IVIB in the literature[11] and the 2015 review of the literature,[8] the published body of knowledge on IVIB continues to grow. It is important to note that some of these studies were open-label investigations, and this study design could have influenced the analgesic outcomes. This review updates the reader on the literature published from 2010 through 2019 regarding this nonopioid modality and summarizes the current findings on the tolerability and efficacy of IVIB and the use of IV morphine.

MATERIALS AND METHODS

A literature search of the National Library of Medicine database and pain-management journals for articles and abstracts published in English was performed utilizing the key words *intravenous ibuprofen, NSAIDs for perioperative pain management,* and *opioid-free surgery*. The narrative review with safety-related implications are detailed as updated from the previously published 2015 tolerability analysis.[8]

RESULTS

The literature search identified 9 clinical studies that met the inclusion criteria for this review. In total, 1062 adult patients and healthy volunteers were included in these 9 studies; 757 of these subjects received IVIB, and the remaining 305 received either placebo or a comparator medication.

Study 1

Singla et al[13] determined whether IVIB could decrease pain and morphine use when compared to placebo. They randomized 185 adult patients undergoing elective orthopedic surgery to receive either IVIB 800 mg or IV placebo (saline) q6h,

* Trademark: Caldolor® (Cumberland Pharmaceuticals Inc, Nashville, Tennessee).

Table 1. IVIB comparison studies in adults.

Study	IVIB, n	Comparator, n	Design	Treatments	IVIB Infusion Time, min	Initiation of IVIB Dosing Relative to Surgery	Description
Singla et al[13]	99	86	MC, rand, DB, PC, MD	IVIB 800 mg vs placebo IV (saline), q6h	NA	Preoperative	Efficacy of pre- and postoperative administration of IVIB in pain control and decreased morphine use in orthopedic surgical patients
Pavliv et al[23]	6	6	SC, rand, DB, PC, SD, crossover	IVIB 800 mg + placebo PO vs ibuprofen 800 mg PO + placebo IV (saline)	5–7 min	NA	Evaluate pharmacokinetics, safety, and tolerability of a single dose of IVIB compared to oral ibuprofen in healthy volunteers
Le et al[24]	28	27	MC, P, rand, DB, PC, SD	IVIB 800 mg vs placebo IV (saline) preoperatively	NA	Preoperative	Examine the effects of preoperative IVIB on stress response and recovery in patients undergoing laparoscopic cholecystectomy
Shepherd et al[25]	28	34	SC, rand, DB, PC, MD	IVIB 800 mg vs placebo IV (saline), followed by scheduled medication with study drug IV + acetaminophen 100 mg PO + bowel care regimen	NA	Intraoperative	Report postoperative pain scores following trans-sphenoidal surgery, determine if multimodal opioid-minimizing pain regimens provide satisfactory postoperative pain control, and determine if IVIB improves

Table 1. (*Continued*)

Study	IVIB, n	Comparator, n	Design	Treatments	IVIB Infusion Time, min	Initiation of IVIB Dosing Relative to Surgery	Description
							postoperative pain scores and decreases opioid use compared with placebo
Viswanath et al[26]	19	22	SC, P, rand, SB, SD	IVIB 800 mg vs acetaminophen 1000 mg IV	30 min	Preoperative	Efficacy of IVIB compared with IV acetaminophen in preemptive analgesia, and determine if there is a difference in the amount of pain medication consumed postoperatively after third molar surgery
Uribe et al[27]	20	31	SC, rand, DB, PA, AC	IVIB 800 mg 2 h before surgery and 4 h after the first dose if not discharged, and ketorolac 30 mg IV at the end of surgery per manufacturer	NA	Preoperative and 4 h after first dose if not discharged	Efficacy of IVIB compared with IV ketorolac and assessment of opioid consumption in arthroscopic knee surgery patients
Bergese et al[15]	150	NA	MC, OL, MD, CSS	IVIB 800 vs 400 mg	5—10 min	NA	Determine the safety and efficacy of IVIB administered over 5—10 min for the treatment of pain or fever in hospitalized patients

(*continued on next page*)

Table 1. (*Continued*)

Study	IVIB, n	Comparator, n	Design	Treatments	IVIB Infusion Time, min	Initiation of IVIB Dosing Relative to Surgery	Description
Gan et al[16]	300	NA	MC, OL, MD, CSS	IVIB 800 mg at anesthesia induction, followed by up to 3 doses postoperatively administered q6h, depending on patient need	5—10 min	Preoperative and postoperative	Determine the safety of single and multiple doses of IVIB administered over 5—10 min at the induction of anesthesia and after the surgical procedures for the treatment of postoperative pain
Martinez et al[28]	107	99	MC, rand, DB, PC, PA	IVIB 800 mg/200 mL or placebo IV (saline 200 mL) on surgical skin closure, followed by q6h up to 24 h (abdominal surgery), 48 h (hip-shoulder-ligament surgery), or 72 h (knee or spine surgery)	15 min	Postoperative	Evaluate the efficacy and tolerability of a new formulation of IVIB for the management of postoperative pain in a European population

AC = active comparator; CSS = clinical surveillance study; DB = double blind; IVIB = intravenous ibuprofen; MC = multicenter; NA = not applicable; OL = open label; P = prospective; PA = parallel group; PC = placebo controlled; rand = randomized; SB = single blind; SC = single center; SD = single dose.

beginning with a preoperative dose at the induction of anesthesia, with access to IV morphine after surgery. The dose (800 mg) of IVIB is the standard and recommended dose for pain management according to the labeling approved by the US Food and Drug Administration and is to be infused over 30 min.[7] The efficacy of IVIB was measured using a visual analog scale (VAS) (assessing pain with movement [VASM] and pain while resting [VASR]) and a verbal response scale (VRS). The amount of morphine used postoperatively was also measured.

In study participants who received IVIB, there was a 26% reduction in VASM score, a 32% reduction in VASR score, and a 20% reduction in VRS score compared to those in patients who received placebo (all, $P < 0.001$). Study participants receiving IVIB also used 31% less morphine than did those who received placebo ($P < 0.001$). A previous randomized, placebo-controlled study in surgical patients concluded that IVIB 800 mg administered q6h was associated with reductions in pain and morphine use[11]; however, Singla et al[13] were the first to study the preoperative administration of IVIB. In addition, the AEs that occurred in the study by Singla et al[13] were similar, with respect to prevalence and intensity, to those reported by Southworth et al.[8]

These authors concluded that the administration of IVIB in a rapid infusion immediately prior to surgery (ie, at the induction of anesthesia) assisted in the down-regulation of proinflammatory pain mediators, and that pre- and postoperative administration of IVIB was associated with significant decreases in pain and morphine use in adult patients undergoing orthopedic surgery.

Study 2

Pavliv et al[23] evaluated the pharmacokinetic properties and tolerability of a rapid infusion of IVIB in healthy adults. They randomized 12 healthy adults to receive a single dose of IVIB 800 mg (infused over 5−7 min) + oral placebo, or oral ibuprofen 800 mg + IV placebo (saline). Blood samples were taken throughout the 12 h after each dose. While the 12 study participants were randomized into 2 groups, on completion of the first dose of study medication, they underwent a 6-day washout period and then received the treatment they had not been administered previously. Thus, all 12 participants received IVIB.

The pharmacokinetic analysis of the samples revealed that the plasma ibuprofen concentration with IVIB was ~2-fold that with oral ibuprofen. Maximum concentration was achieved in 0.11 h (6.5 min) by the end of the infusion with IVIB versus 1.5 h with oral ibuprofen. The $t_{1/2}$ was 2 h with IVIB and oral ibuprofen, and both were 100% bioavailable. The concerns about tolerability with the rapid IVIB infusion did not materialize, as there were no significant differences in these parameters compared to oral ibuprofen. Four study participants noted discomfort at the infusion site with IVIB, which was of mild intensity; with oral ibuprofen, 1 study participant had a mild hematoma and another had mild epistaxis. There were no treatment-emergent serious AEs (SAEs).

The limitations of this study included the lack of a direct comparison with IVIB given over a 30-min period, a lack of measurement of GI and renal effects, and the possibility that rapidly infused IVIB could affect critically ill and postoperative patients differently versus this group of healthy subjects.

These authors concluded that rapid-infusion (5−7 min) IVIB in healthy adults reached a higher plasma concentration more quickly than did the oral formulation, and was well tolerated, with no treatment-emergent SAEs reported.

Study 3

Le et al[24] observed the effects of preoperative IVIB on stress response and postoperative recovery in 55 adult patients preparing for laparoscopic cholecystectomy. Patients were randomized to receive a preoperative dose of IVIB 800 mg or IV placebo (saline). Neurobehavioral assessments included the 40-item Quality of Recovery (QoR40) questionnaire, the 9-item Modified Fatigue Severity Scale, and the 15-item Geriatric Depression Scale (GDS) for the evaluations of recovery, fatigue, and mood, respectively. Treatment was administered preoperatively, postoperatively in the postanesthesia care unit (PACU), and on postoperative days (PODs) 1 and 3. Blood samples were taken before the study drug was administered, intraoperatively, and postoperatively for the measurement of cytokines (tumor necrosis factor-α; interleukins [IL] 1β, 2, 6, and 10; and interferon-γ), cortisol, C-reactive protein, epinephrine, and norepinephrine.

The results of the study showed that the QoR40 score in the IVIB group remained at a near-baseline level, while the score in the placebo group was decreased (worsened) ($P < 0.001$). Fatigue severity did not significantly change in the IVIB group in the 4 testing periods, but was increased (worsened) in patients receiving placebo. The placebo group had lower GDS scores versus baseline on POD 3, but there was no significant difference between the IVIB and placebo groups in any test period. Cortisol level was increased versus baseline in both groups intraoperatively, but were lower in the PACU in the IVIB group ($P = 0.001$); there was no difference in C-reactive protein between groups. Epinephrine level was lower in the IVIB group intraoperatively ($P = 0.004$), and while low in both groups in the PACU, there was no difference between groups. Norepinephrine levels were lower in the IVIB group intraoperatively ($P = 0.004$), but no difference was seen between the groups in the PACU. Some of the cytokine concentrations could not be detected in the samples and, therefore, no analysis could be performed. However, IL-10 was increased in the placebo group after surgery ($P < 0.001$), with no change in the IVIB group, but the IL-10 concentration was significantly lower in the IVIB group versus placebo in the PACU ($P < 0.001$). Tumor necrosis factor-α in the IVIB group was significantly higher intraoperatively compared to that in the placebo group ($P < 0.001$). IL-6 concentration was not significantly different between the groups at any sampling time.

A limitation of this study was that the amount of opioid given during surgery could not be standardized due to the multiple centers and anesthesia providers. Despite this, no significant difference in opioid use was detected between the groups, which allowed for an objective examination of the effects of IVIB independent of opioid administration. Another limitation was the QoR40 score used for assessing the quality of recovery; this score is reliable and valid for short-term patient recovery, but cognition is not assessed comprehensively, and this score does not define recovery in individual patients.

These researchers concluded that the addition of IVIB prior to surgery improves the quality of recovery, reduces postsurgical fatigue, and reduces surgical stress response.

Study 4

Shepherd et al[25] measured postoperative pain; quantified the efficacy of multimodal, opioid-minimizing pain management relative to the adequacy of postoperative pain control, and quantified postoperative pain and opioid use for comparisons between IVIB and IV placebo (saline). They randomized 62 adult patients undergoing transsphenoidal surgery for pituitary tumors to receive oral acetaminophen plus either IVIB or IV placebo, with rescue opioids given as needed in both groups. The primary end point was patient-reported pain as measured on a VAS (0−10) every 4 h for 48 h after surgery. The secondary end point was a quantification of opioid use as estimated by oral morphine equivalents for the same timeframe. Other outcomes assessed included length of stay, requirement of antiemetics, and the number of bowel movements while hospitalized.

With both pain-management protocols, acceptable postoperative pain relief was achieved. However, there were reductions of 43% and 58% in pain score and opioid use, respectively, in the IVIB group compared with those in the placebo group. Two AEs (discomfort at the injection site and postoperative hyperkalemia), but no bleeding complications, were reported with IVIB, while 2 cases of delayed epistaxis occurred in the placebo group.

The study limitations included a lack of balance in patient ages (pain scores were analyzed using age as a covariate to account for this limitation), and a lack of power to detect between-group differences in rare bleeding complications, as ibuprofen is a cyclooxygenase-2 inhibitor that could alter platelet function. There were no bleeding complications reported despite this limitation.

These researchers concluded that the results of this study may be generalized to the healthy population of patients undergoing this type of surgery. The primary results demonstrated that pain control and opioid use were improved with IVIB + acetaminophen compared with IV placebo + acetaminophen in patients undergoing transsphenoidal surgery.

Study 5

Viswanath et al[26] compared the level of postoperative pain after molar extraction in patients

receiving either preoperative IVIB or preoperative IV acetaminophen. They randomized 41 adult patients undergoing surgical extraction of 2 or more third molars to receive either IVIB 800 mg or acetaminophen 1000 mg IV. The primary end point was postoperative pain measured on a VAS at specific time points, and the secondary end point was the amount of postoperative analgesic medication used by patients in each group.

In this study, patients who received IVIB 800 mg preoperatively reported significantly less pain at 4 h ($P = 0.004$), 24 h ($P = 0.019$), and 48 h ($P = 0.017$) postoperatively than did the patients who received 1000 mg IV acetaminophen. At 4 and 24 h postoperatively, the IVIB group reported pain levels of <20 mm on the VAS. There continued to be a reduction in reported pain in the IVIB group at 72 h when compared to that in the IV acetaminophen group, although statistical significance was lost at 72 h (which is unsurprising as the half-life of ibuprofen approximates 2 h). The IVIB group used fewer opioid medications than did the IV acetaminophen group ($P = 0.005$), and, after adjustment for potential confounders, the difference continued to be statistically significant ($P = 0.009$). The amount of over-the-counter analgesics in the 10-day postoperative period taken by the IVIB group compared to the IV acetaminophen group was also less, but the difference was not statistically significant. No intraoperative or postoperative AEs were reported.

A limitation of this study was the small sample size due to a substantial number of patients who were lost to follow-up. This could have been prevented by recalling the patients for a 2-day follow-up or increasing the number of patient reminders. No additional patients were recruited because statistically significant results had already been achieved and the researchers' institutional review board denied additional enrollment.

These researchers concluded that preoperative IVIB was more efficacious postoperatively, with decreased pain and use of opioids, when compared with preoperative IV acetaminophen.

Study 6

Uribe et al[27] compared the efficacy of IVIB and IV ketorolac in the treatment of postoperative pain in 51 randomized adult patients undergoing arthroscopic knee surgery. Patients received either IVIB 1600 mg (given as divided 800-mg doses) or ketorolac 30 mg IV (given as a single dose). Patients in the IVIB group received 800 mg within 2 h preoperatively and an additional 800-mg dose 4 h after the first dose if they were still hospitalized. Patients in the IV ketorolac group received 30 mg at the end of surgery per the manufacturer's instructions.[29] Pain was assessed via median VAS at rest and on movement on arrival at the PACU, and opioid use was measured for up to 24 h postoperatively.

On patient arrival at the PACU, pain scores at rest were 33 versus 9 ($P = 0.0064$), and on movement were 38 and 15 ($P = 0.0018$) in the IV ketorolac and IVIB groups, respectively. Pain scores on movement taken at 30-min intervals in the IVIB group were less than half of those reported in the IV ketorolac group for 1.5 h after PACU arrival. During the PACU timeframe, opioid medication use was required in 55.0% of the IVIB group versus 83.9% of the IV ketorolac group, with the mean amount of oral morphine use being higher in the IV ketorolac group versus the IVIB group ($P < 0.001$).

The study design was a limitation, as this pilot study had no control group or power analysis; however, on unblinding at study conclusion, the patients were divided in a 3:2 ratio between the ketorolac and ibuprofen groups, respectively. Another limitation of the study was that the design was created regarding the label administration, which introduced a confounder regarding the fact that preemptive systemic ibuprofen was already present at the time of surgery due to when the IVIB was given. These limitations could have interfered with the results of the postoperative pain and opioid-use assessments.

The researchers concluded that preemptive use of IVIB 800 mg decreased postoperative pain and opioid use compared with ketorolac IV in patients undergoing arthroscopic knee surgery.

Study 7

Bergese et al[15] studied the tolerability and efficacy of IVIB administered over 5−10 min for the treatment of pain or fever in hospitalized patients. Until this study, the prior literature had reflected studies utilizing 30-min infusion times. A more rapid infusion might yield additional benefits, particularly in cases in which time is of the essence, such as in the emergency department in patients sustaining trauma,

or in febrile patients. This Phase IV, multicenter (13 US centers), open-label clinical surveillance study enrolled a total of 150 adult hospitalized patients. End points were AEs as reported by patients, decrease from baseline in temperature in febrile patients, and change from baseline in pain scores on a VAS.

The most common AEs experienced by participants were infusion-site pain, in 22 patients (15%; 4 patients [3%] discontinued the study drug due to this AE), and flatulence, in 8 (5%). In patients with fever, temperature was decreased from baseline at 4 h (mean [SD] reduction, 0.8 [0.69] °C). In patients with pain, patient-reported VAS scores were decreased from baseline over 4 h (mean [SD] reduction, 27.1 [31.29] mm).

The limitations of this study included the lack of a control arm, the use of additional analgesics and antipyretics before the study drug was administered, and the wide range of pain types and differences in efficacy of ibuprofen based on the treatment of pain of different etiologies.

The study demonstrated that more rapid administration of IVIB was well tolerated and was an effective treatment for pain and fever in hospitalized US patients.

Study 8

Gan et al,[16] in a follow-up to the study by Bergese et al,[15] applied a protocol of rapid IVIB infusion to evaluate opioid requirements associated with surgical and postoperative pain. This Phase IV, multicenter (21 US hospitals), open-label, clinical surveillance study was conducted in 300 adult hospitalized patients. Patients received IVIB 800 mg of administered over 5−10 min preoperatively.

Of the 300 study participants, 252 received a single dose of IVIB preoperatively, and 48 received ≥2 doses preoperatively and postoperatively. A total of 65 study participants (22%) reported AEs (serious and nonserious). The most common AE was infusion-site pain (34 patients [11%]). No deaths were reported. Nine patients reported SAEs, 8 of which occurred during the first 6 h. All SAEs reported were considered by the investigators as unrelated to ibuprofen. Two patients (0.67%) discontinued the study drug due to an AE (1 due to infusion-site pain and 1 due to a hypersensitivity reaction after drug administration).

The limitations of this study included the lack of a control group; the lack of assessment of change in renal function before and after surgery; and the lack of control of the type of surgical procedure, anesthesia protocol, and pain regimen. The variability in surgery types did allow for a more broad assessment of the tolerability and efficacy of IVIB in these settings.

This study demonstrated that IVIB infused over 5−10 min at the induction of anesthesia is a well-tolerated administration option in surgical patients.

Study 9

Martinez et al[28] replicated the methodology and findings of a Phase II dose-ranging study originally reported by Southworth et al.[11] This study revalidated the efficacy and safety profiles of IVIB for the management of postoperative pain in a European population.

A total of 206 patients undergoing abdominal and orthopedic surgery were randomly assigned in a 1:1 ratio to receive IVIB 800 mg or IV placebo (saline) q6h; all patients had access to morphine through a patient-controlled analgesia pump. The primary end point was the median amount of morphine used within the first 24 h postoperatively. The mean (SEM) of morphine requirements was reduced from 29.8 (5.25) mg to 14.22 (3.23) mg ($P = 0.015$), and there were decreases in pain at rest as measured on a VAS, from 3.34 (0.35) to 0.86 (0.24) ($P = 0.02$), and during movement, from 4.32 (0.36) to 1.90 (0.30) ($P = 0.02$), in the IVIB treatment group, while in the placebo group, VAS score at rest was decreased from 4.68 (0.40) to 2.12 (0.42), and during movement, from 5.66 (0.42) to 3.38 (0.44. The prevalences of AEs were similar between study groups, with no statistical difference in the overall prevalence of these events.

The limitations of this study included the small sample size and projected morphine use. The inability to include more patients undergoing orthopedic surgery, as originally intended, lowered the number of study patients and the VAS score prediction of severe postoperative pain—the researchers were unable to assess the effectiveness of IVIB in pain management in this type of surgery, to draw conclusions regarding the use of IVIB in a 72-h period, or to assess the benefit of decreased morphine use postsurgery.

With perioperative administration of IVIB 800 mg q6h in patients undergoing abdominal surgery, pain and morphine requirements were decreased, reconfirming that IVIB was well tolerated in this adult population.

DISCUSSION

Of the 9 studies analyzed, 4 (Singla et al,[13] Shepherd et al,[25] Viswanath et al,[26] and Uribe et al[27]) investigated the efficacy of IVIB using pain scores and postoperative opioid use. IVIB was reproducibly more effective in reducing postoperative pain and the quantity of opioids used than were placebo, IV acetaminophen, an analgesic regimen with placebo, oral acetaminophen, and IV ketorolac in patients undergoing orthopedic, trans-sphenoidal, third molar, and arthroscopic knee surgery, respectively.

In the study by Singla et al,[13] 90 of 99 IVIB-treated patients (91%) experienced AEs—45 of mild, 39 of moderate, and 6 of severe intensity. In the patients receiving placebo, 74 of 86 (86%) experienced AEs—36 of mild, 37 of moderate, 1 of severe intensity. There were no statistical differences in the intensity of AEs between the treatment groups ($P = 0.356$). When comparing the numbers of patients experiencing severe AEs in the IVIB group versus the placebo group, there was no significant statistical difference ($P = 0.507$). In the 3 remaining studies, there was no significant statistical difference between the groups studied with regard to AEs.

Pavliv et al[23] studied the pharmacokinetic properties and tolerability of IVIB and reported that rapid-infusion IVIB administration was associated with a more rapidly increased plasma concentration than was oral ibuprofen (achieving a 2-fold increase in C_{max}), and was well tolerated, in healthy subjects. While this study did not address rapid infusions in critically ill or postoperative patients, it was hypothesized that poor tolerability in these patients would be unlikely, based on the data that 30- to 60-min IVIB infusions were well tolerated and effective in this population. AEs occurred in 4 subjects receiving IVIB and in 2 receiving oral ibuprofen ($P = 0.355$), but were of mild intensity (ie, infusion-site pain [IVIB] and hematoma and epistaxis [oral ibuprofen]). No SAEs or deaths were reported.

Le et al[24] examined stress response and postoperative recovery in patients receiving IVIB compared to placebo. The addition of an NSAID improved quality of recovery, lessened postsurgical fatigue, and enhanced early postoperative outcomes as reported by the study patients. The patients receiving IVIB had decreased levels of catecholamines, cortisol, and cytokines, indicating curbed stress and inflammatory response.

Bergese et al[15] and Gan et al[16] validated the tolerability and efficacy of shortened infusion times of IVIB. The implications of these parallel studies are several-fold. First, rapid infusion of IVIB (5−10 min administration times) will not delay the induction of a patient about to undergo anesthesia and surgery. Second, rapid-infusion IVIB shortens the relief time in trauma patients in the emergency department setting in whom time is of the essence, and the patient experience is an important component of customer-satisfaction scores reported by hospitals. Third, rapid infusion IVIB is well tolerated in febrile patients and can be utilized in adults for all-cause febrility where reduction of fever is a crucial element of minimizing febrility-associated symptoms and side effects.

The original tolerability and efficacy reporting of IVIB was first published in a predominantly US-based patient population,[11] but has now been reproduced in a Phase III trial in 206 European adult patients.[28] The study reported statistically significant reductions in opioid use and delivery and patient-reported VAS scores in postoperative patients at rest and during activity.

CONCLUSION

Pain of surgical or traumatic origin is a common reason for the initiation of analgesic treatment, but several self-evident, but often unstated, concerns about opioids bear consideration. Opioids provide no antiinflammatory benefit; no locally analgesic effect, acting solely within the CNS; no antipyretic effect; and no benefit against the injury or disease pathology itself. Despite these limitations, opioids have been a mainstay in the initial treatment of patient-reported trauma- and surgery-related pain for decades. Monotherapy utilizing opioids, therefore, may not serve the best interests of patients based on their associated AEs and potential for diversion, tolerance, and abuse (even with short-term use). It is incumbent on physicians, as stewards of health and safety, to become subject-matter experts in multimodal pain-treatment options that de-emphasize opioids. Evidence-based analgesia techniques may involve few

or multiple components but need not be complex. Judicious use of nonopioid and opioid therapies must be tailored to the needs of the patient. Preemptive IVIB should be considered in the analgesic regimen for the management of peri- and postoperative pain and pain of traumatic origin, as it has a favorable safety profile, with fewer associated AEs, and provides satisfactory pain control with decreased use of opioid medications.

ACKNOWLEDGMENTS

Funding Support

This research was supported, in a small part, by Cumberland Pharmaceuticals, Inc., USA. Cumberland did not participate in the concept, development, data analysis, narrative review, or any part of the writing or submission of the manuscript.

Author Contributions

The authors made substantial contributions to all of the following: conception and design of the study, analysis and interpretation of the data, drafting of the manuscript or revising it critically for important intellectual content (S. Southworth: conceptualization, methodology, resources, writing, review and editing, supervision; J. Sellers: methodology, writing of the original draft, visualization, project administration). The authors approved the final version of the submitted manuscript.

Disclosures

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

REFERENCES

1. Centers for Disease Control and Prevention. *Understanding the Epidemic*; 2016. Available at: https://www.cdc.gov/drugoverdose/epidemic. Accessed October 24, 2019.
2. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008;11(Suppl):S63–S88.
3. Warner M, Chen LH, Makuc DM, et al. *Drug Poisoning Deaths in the United States, 1980–2008. NCHS Data Brief No. 81*. Hyattsville, Md: National Center for Health Statistics; 2011.
4. Paulozzi LJ, Jones CM, Mack KA, et al, Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60:1487–1492.
5. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA*. 2013;309:657–659.
6. Enhanced recovery after surgery society guidelines. Available at: http://erassociety.org/2015. Accessed October 24, 2019.
7. *Caldolor (Ibuprofen) Injection [package Insert]*. Nashville, Tenn: Cumberland Pharmaceuticals Inc; 2015.
8. Southworth SR, Woodward EJ, Peng A, et al. An integrated safety analysis of intravenous ibuprofen (Caldolor) in adults. *J Pain Res*. 2015;8:753–765.
9. Morris PE, Promes JT, Guntupalli KK, et al. A multi-center, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for the treatment of fever in critically ill and noncritically ill adults. *Crit Care*. 2010;14:R125.
10. Krudsood S, Tangpukdee N, Wilairatana P, et al. Intravenous ibuprofen (IV-ibuprofen) controls fever effectively in adults with acute uncomplicated *Plasmodium falciparum* malaria but prolongs parasitemia. *Am J Trop Med Hyg*. 2010;83:51–55.
11. Southworth S, Peters J, Rock A, et al. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clin Ther*. 2009;31:1235–1922.
12. Kroll PB, Meadows L, Rock A, et al. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (iv-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. *Pain Prac*. 2011;11:23–32.
13. Singla N, Rock A, Pavliv L. A multi-center, randomized, double-blind, placebo-controlled trial of intravenous-ibuprofen (IV-ibuprofen) for treatment of pain in post-operative orthopedic adult patients. *Pain Med*. 2010;11:1284–1293.
14. Promes JT, Safcsak K, Pavliv L, et al. A prospective, multicenter, randomized, double-blind trial of IV ibuprofen for treatment of fever and pain in burn patients. *J Burn Care Res*. 2011;32:79–90.
15. Bergese SD, Candiotti K, Ayad SS, et al. The shortened infusion time of intravenous ibuprofen part 1: a multicenter, open-label, surveillance trial to evaluate safety and efficacy. *Clin Ther*. 2015;37:360–367.
16. Gan TJ, Candiotti K, Turan A, et al. The shortened infusion time of intravenous ibuprofen, part 2: a multicenter, open-label, surgical surveillance trial to evaluate safety. *Clin Ther*. 2015;37:368–375.

17. Cumberland Pharmaceuticals Inc. A pilot study to determine the efficacy of intravenous ibuprofen for pain control following arthroscopic knee surgery. NLM identifier: NCT01650519. Available at: https://clinicaltrials.gov/ct2/show/NCT01650519. Accessed October 24, 2019.
18. Cumberland Pharmaceuticals Inc. Efficacy of intravenous ibuprofen compared to intravenous ketorolac for pain control following arthroscopic knee surgery. NLM identifier: NCT01901393. Available at: https://clinicaltrials.gov/ct2/show/NCT01901393?term=NCT01901393&rank=1. Accessed July 5, 2019.
19. van Hecken A, Schwartz JI, Depre M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. *J Clin Pharmacol*. 2000;40:1109–1120.
20. Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and upper gastrointestinal complications: a systemic review and meta-analysis of observational studies (the SOS project). *Drug Saf*. 2012;35:1127–1146.
21. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med*. 2011;8:e1001098.
22. Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, et al. Risk of hospitalizations for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med*. 1998;158:33–39.
23. Pavliv L, Voss B, Rock A. Pharmacokinetics, safety, and tolerability of a rapid infusion of I.V. ibuprofen in healthy adults. *Am J Health-Syst Pharm*. 2011;689:47–51.
24. Le V, Kurnutala L, Schiano Di Cola J, et al. Premedication with intravenous ibuprofen improves recovery characteristics and stress response in adults undergoing laparoscopic cholecystectomy: a randomized controlled trial. *Pain Med*. 2016;17:1163–1173. https://doi.org/10.1093/pm/pnv113. Available at: . Accessed October 24, 2019.
25. Shepherd D, Jahnke H, White W, et al. Randomized, double-blinded, placebo-controlled trial comparing two multimodal opioid-minimizing pain management regimens following transsphenoidal surgery. *J Neurosurg*. 2017;128:329–659.
26. Viswanath A, Oreadi D, Finkelman M, et al. Does pre-emptive administration of intravenous ibuprofen (Caldolor) or intravenous acetaminophen (Ofirmev) reduce postoperative pain and subsequent narcotic consumption after third molar surgery? *J Oral Maxillofacial Surg*. 2019;77:262–279. https://doi.org/10.1016/j.joms.2018.09.010. Available at: . Accessed October 24, 2019.
27. Uribe A, Arbona F, Flanigan DC, et al. Comparing the efficacy of IV ibuprofen and ketorolac in the management of postoperative pain following arthroscopic knee surgery. A randomized double-blind active comparator pilot study. *Front Surg*. 2018;5. https://doi.org/10.3389/fsurg.2018.00059. Article 59. Available at: . Accessed October 21, 2019.
28. Martinez A, Rodriguez B, Roca A, et al. Intravenous ibuprofen for treatment of post-operative pain: a multicenter, double blind, placebo-controlled, randomized clinical trial. *PLoS One*. 2016;11:e0154004.
29. *Toradol (Ketorolac tromethamine injection, USP) [package insert]*. Lake Forest, IL: Hospira, Inc.; 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/074802s038lbl.pdf. Accessed May 27, 2020.

Address correspondence to: Jill A. Sellers, BSPharm, PharmD, 1200 East Woodhurst, Building L Suite 100, Springfield, MO, 65804, USA. E-mail: jill@medavera.com