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PRS GLOBAL OPEN

ORIGINAL ARTICLE
Reconstructive

Standardized Perioperative Protocol and Routine Ketorolac Use for Head and Neck Free Flap Reconstruction

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Background: No consensus exists on ideal perioperative management or anticoagulation regimen for free flap reconstruction of the head and neck. Perceived benefits from antiplatelet therapy need to be balanced against potential complications. Ketorolac, a platelet aggregation inhibitor and a parenteral analgesic, was introduced as part of a standardized perioperative protocol at our institution. In this study, we aimed to examine the impact of implementation of this protocol as well as complications associated with the routine use of perioperative ketorolac in a diverse group of patients who underwent head and neck free flap reconstruction.
Methods: A single institution retrospective review was performed, including all patients who underwent head and neck free flap reconstruction between October 2016 and November 2019. Patients were divided into two cohorts: those who received ketorolac as part of a standardized protocol, and those who did not.
Results: Twenty-four consecutive patients with 24 head and neck free flaps were evaluated. Eighteen patients were in the standard protocol, and six were not. There were no microvascular thromboses, flap failures, or hematomas in either group. Intensive care unit length of stay and opiate use were significantly reduced in the standardized protocol group.
Conclusions: A standardized perioperative protocol for head and neck free flap reconstruction can reduce hospital and intensive care unit length of stay. No statistically significant differences in complication rates were identified when comparing ketorolac use and perioperative regimens among patients undergoing a diverse set of microsurgical head and neck free flap reconstructions. *(Plast Reconstr Surg Glob Open 2022;10:e4318; doi: 10.1097/GOX.0000000000004318; Published online 11 May 2022.)*

INTRODUCTION

Microvascular free flap reconstruction has become standard of care for many complex head and neck defects resulting from tumor ablation and trauma.[1] Local and systemic complications can be devastating, adding morbidity to usually prolonged postoperative courses. Surgical techniques and perioperative management have significantly evolved so as to herald free flap success rates over 90%.[2,3] Although a rare complication, total flap loss is most often caused by microvascular thrombosis.[2,4] Many medications such as heparin, low weight molecular heparin, aspirin, and dextran have been studied for postoperative flap prophylactic anticoagulation after microsurgical procedures[1,4]; still, an ideal antithrombotic regimen in head and neck free flap reconstruction is yet to be established.[1,4–6]

Postoperative pain management for patients undergoing head and neck free flaps also remains challenging. Enhanced Recovery After Surgery (ERAS) protocols have recently focused on optimal analgesia for these patients with tenuous aerodigestive pathways and fluid statuses.[5] The ERAS society recommends a multimodal approach, emphasizing premedication with nonsteroidal antiinflammatory drugs (NSAIDs) to decrease reliance on opioids.[5] Prior studies have demonstrated postoperative multimodal analgesia with ketorolac (Toradol, F. Hoffman – La Roche Ltd, Nutley, N.J.) to significantly decrease the need for opiates in head and neck free flap patients.[7] Ketorolac

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Received for publication January 3, 2022; accepted March 30, 2022.

DOI: 10.1097/GOX.0000000000004318

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

also inhibits platelet aggregation, making it a desirable pharmaceutical adjunct in free flap tissue transfer.[8]

Widespread use of the NSAID ketorolac in clinical practice has been hampered by concerns for postoperative bleeding. In this investigation, we report our institution's experience with routine ketorolac use as part of a standardized perioperative protocol in addition to deep vein thrombosis chemoprophylaxis for patients undergoing microvascular free tissue transfer to the head and neck.

Takeaways

Question: Does perioperative standardization improve outcomes for head and neck free flap reconstruction?

Findings: Twenty-four consecutive patients were evaluated, including 18 with standardized perioperative protocol, and six without. There were no flap failures. ICU length of stay and opiate use were significantly reduced in the standardized perioperative protocol group. No differences in local or systemic complications were found.

Meaning: A standard perioperative approach with routine ketorolac use for patients undergoing head and neck free flap reconstruction is safe and can reduce length of stay and improve pain control.

METHODS

Institutional review board approval was obtained for a retrospective chart review of all patients who underwent a microvascular free tissue transfer to the head/neck region between October 2016 and November 2019 at a single institution. Data (including patient demographics, comorbidities, primary diagnosis, surgical ablation, type of reconstruction, perioperative ketorolac use, overall hospital and intensive care unit (ICU) length of stay (LOS), opiate use, and complications) were extracted from hospital and outpatient medical records. Ablative procedures were performed by four surgeons from three specialties (otolaryngology, surgical oncology, and neurosurgery). All free flap reconstructions were performed in an immediate fashion by one of the two plastic surgeons (J.C.S. and R.L.A.). In 2018, in an effort to standardize and coordinate perioperative care across multiple specialties, a head and neck reconstruction perioperative protocol was adopted incorporating the routine use of ketorolac (Fig. 1). The perioperative protocol included coordinated case preparation between ablative surgeon, plastic surgeon, and anesthesia, as well creation of an intraoperative checklist (Fig. 2), and postoperative emphasis on early mobilization, reducing ICU stay, and de-emphasizing opiate use through multimodal pain regimen. A 15-mg dose of ketorolac was given intraoperatively at the time of microanastomosis and every 6 hours thereafter for a maximum of 5 days. Thus, patients in this series were divided into two cohorts—those who underwent head and neck free flap reconstruction before the protocol, and those after. Some of the patients in the cohort before implementing a standard perioperative protocol received daily aspirin as an alternative antiplatelet per the surgeon's discretion, while none received ketorolac. All patients were treated with deep vein thrombosis chemoprophylaxis of heparin or LMWH throughout their admissions in addition to antiplatelet therapy.

Postoperative opiate use was calculated by converting administered medications into morphine milligram equivalents (MME). Average daily MME was calculated for the first 5 days postoperatively, corresponding to the maximum length of ketorolac administration.

Surgical complications were characterized as related to either donor or recipient sites. Specific complications measured included microvascular thrombosis, flap necrosis (total and partial), hematoma, seroma, infection, skin graft failure, and wound dehiscence. Systemic complications within the first 30 postoperative days were also analyzed, including acute kidney injury, pneumonia, cardiac events, thromboembolic events, sepsis, cancer recurrence, and 30-day mortality.

SPSS (IBM SPSS Statistics for Macintosh, version 25.0.; IBM Corp, Armonk, N.Y.) software was employed for statistical evaluation. All variables were compared using Student *t*-test. Statistical significance was defined as a P value less than 0.05.

RESULTS

Twenty-four head and neck free flaps were performed in 24 consecutive patients; all patients were included in our study. The mean duration of follow up was 7.9 months. Eighteen patients were treated after the implementation of a standardized perioperative protocol and received ketorolac; six patients were treated prior, and did not receive ketorolac. There were no statistically significant differences in comorbidities between the two cohorts, but significantly more patients in the standard protocol group had prior radiotherapy (Table 1). As shown in Table 2, the most common ablative surgery for the standard protocol group was laryngopharyngectomy (4/18 or 22.2%), while hemiglossectomy and composite oral resections were the two most prevalent ablative surgeries for the nonstandardized group (2/6 or 33.3%, each). Three patients in the standardized protocol cohort did not have a diagnosis of cancer, whereas all patients in the nonstandardized group underwent oncologic procedures. Nononcologic reconstructions performed include a neurotized free gracilis flap for facial paralysis, a free anterolateral thigh flap after total maxillectomy for fibrous dysplasia, and a radial forearm free flap complex scalp reconstruction following debridement of an infected cranioplasty.

Lateral thigh flaps based on the descending branch of the lateral circumflex femoral artery were the most common flap-type in our series (Table 3). Lateral thigh flaps included anterolateral thigh perforator flaps, vastus lateralis muscle flaps, and chimeric anterolateral thigh/vastus lateralis flaps. In total, 9/18 (50.0%) of standard protocol patients and 3/6 (50.0%) nonstandard patients had reconstruction with a lateral thigh free flap. Radial forearm free flaps were the second most commonly employed flap in the standard protocol (4/18 or 22.3%) and nonstandard (2/6 or 33.3%) groups.

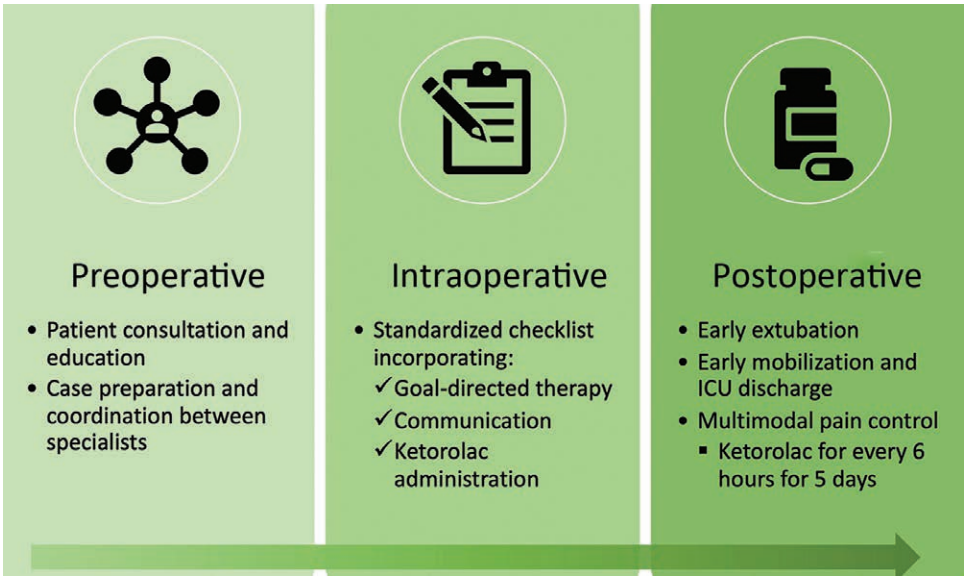

Fig. 1. Flowsheet of head and neck free flap perioperative protocol.

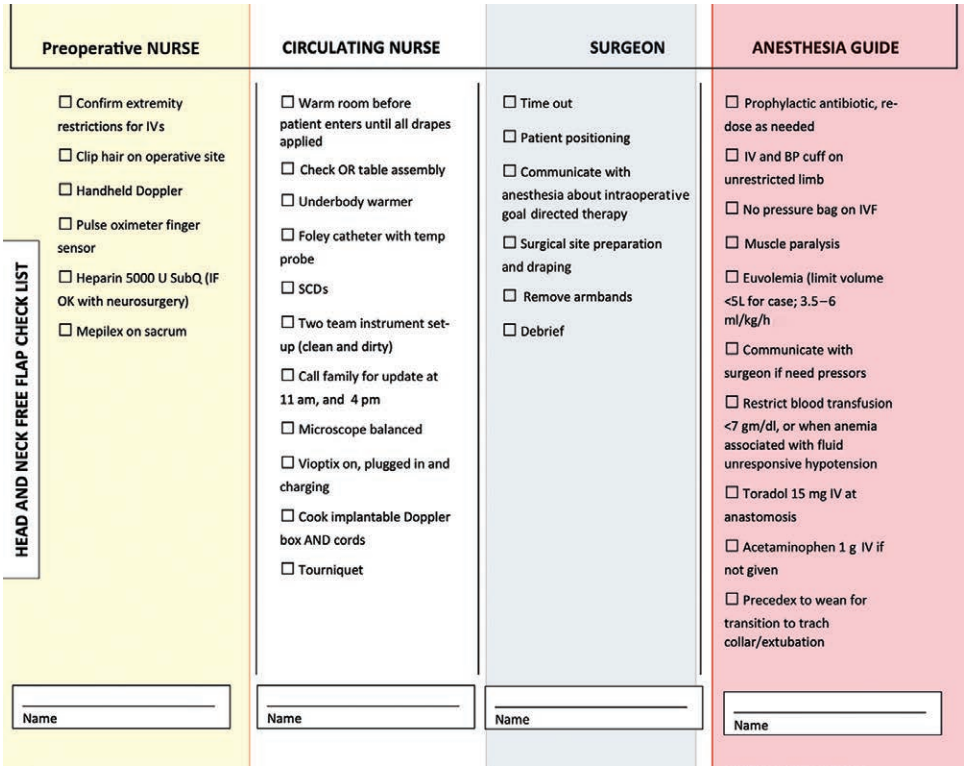

Fig. 2. Intraoperative head and neck free flap checklist.

There were no microvascular thrombotic events and no complete flap losses in either cohort (Table 4). No patients in the standard protocol group and two patients in the nonstandard group demonstrated partial flap necrosis (0% versus 33.3%, $P = 0.054$). The partial flap necroses were considered minor and did not warrant operative intervention. These events were treated with local wound care and went on to heal successfully by secondary intention. There were no postoperative hematomas at the donor or recipient sites.

No significant difference was noted in the rate of donor site seroma formation among patients in the standard versus nonstandard protocol groups (11.1 versus 16.7%, $P = 1.0$). Recipient and donor site infection rates were comparable between groups. One patient in the nonstandard cohort experienced wound dehiscence at the recipient

Table 1. Patient Demographics

	Standard Group, n (%)	Nonstandard Group, n (%)	Total (%)	*P*
No. patients	18	6	24	
BMI	25.3	24.9	25.2	0.897
Age (y)	63.2	59.7		0.641
Gender				
Men	12 (66.7)	5 (83.3)	17	
Women	6 (33.3)	1 (16.7)	7	0.629
Diabetes mellitus	3 (17.6)	1 (16.7)	4 (17.4)	1.000
CAD	1 (5.8)	1 (16.7)	2 (8.7)	0.462
CKD	0 (0)	0 (0)	0 (0)	N/A
Hypertension	6 (35.3)	3 (50)	9 (39.1)	0.643
Hyperlipidemia	5 (29.4)	2 (33.3)	7 (30.4)	1.000
PAD	0 (0)	0 (0)	0 (0)	N/A
Former smoker	12 (70.6)	2 (33.3)	14 (60.9)	0.162
Current smoker	1 (5.8)	1 (16.7)	2 (8.7)	0.462
Asthma	1 (5.8)	0 (0)	1 (4.3)	1.000
Preoperative radiation	8 (44.4)	0 (0)	8 (33.3)	0.024

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; PAD, peripheral arterial disease.

site; this was considered minor and resolved with local wound care. In total, two of 18 standard protocol patients versus zero of six nonstandard patients experienced skin graft loss at the donor site; however, this was not found to be secondary to hematoma or increased bleeding of the wound bed, and no significant difference was seen between groups ($P = 1.0$).

Postoperative systemic complication rates were comparable between the cohorts (Table 5). No patients in either group demonstrated acute kidney injury, defined as an elevation in creatinine from baseline by at least 0.3 mg per dl. Zero patients experienced a deep vein thrombosis; however, one patient in the nonstandard group had a pulmonary embolism diagnosed after discharge from the hospital. One patient from the nonstandard cohort suffered a myocardial infarction that decompensated to cardiac arrest. There were no 30 day mortalities.

Both total hospital LOS and ICU LOS were reduced following implementation of our standard perioperative protocol (Table 6). The total average hospital length of stay in the nonstandard group was 19 days, and 9 days in the standard protocol group ($P = 0.14$). The ICU LOS was significantly reduced between cohorts (13.83 versus 1.5 days, $P = 0.003$). Additionally, opiate use as determined by average MME calculated for the first five postoperative days was significantly less in the standard perioperative protocol group than in the nonstandard group (10.5 mg versus 73.6 mg, $P = 0.001$)

Table 2. Ablative Surgeries

	Standard Group, n (%)	Nonstandard Group, n (%)	Total (%)
No. patients	18	6	24
Wide local excision/craniectomy	3 (16.7)	1 (16.7)	4 (16.7)
Maxillectomy	1 (5.6)	0 (0)	1 (4.2)
Laryngopharyngectomy	4 (22.2)	0 (0)	4 (16.7)
Rhinectomy	1 (5.6)	0 (0)	1 (4.2)
Hemiglossectomy	2 (11.1)	2 (33.3)	4 (16.7)
Orbit exenteration	1 (5.6)	0 (0)	1 (4.2)
Segmental mandibulectomy	2 (11.1)	0 (0)	2 (8.3)
Oromandibular composite resection	2 (11.1)	0 (0)	2 (8.3)
Total glossectomy	0 (0)	1 (16.7)	1 (4.2)
Facial reanimation	1 (5.6)	0 (0)	1 (4.2)
Wide local tissue excision	1 (5.6)	0 (0)	1 (4.2)
Composite oral resection	0 (0)	2 (33.3)	2 (8.3)

Table 3. Free Flap Type

	Standard Group, n (%)	Nonstandard Group, n (%)	Total (%)	*P*
Total	18	6	24	
Latissimus dorsi	0 (0)	1 (16.7)	1 (4.2)	
Lateral thigh	9 (50.0)	3 (50.0)	12 (50.0)	
Radial forearm free	4 (22.2)	2 (33.3)	6 (25.0)	
Fibula	3 (16.7)	0 (0)	3 (12.5)	
MSAP	1 (5.6)	0 (0)	1 (4.2)	
Gracilis	1 (5.6)	0 (0)	1 (4.3)	0.514

MSAP, medial sural artery perforator.

DISCUSSION

Free flap reconstruction has become the gold standard for complex head and neck defects. Although rare, microvascular thrombosis and free flap loss in the head and neck region is a devastating complication, often necessitating the immediate transfer of another free flap or a less-than-ideal regional pedicled flap. Many agents to reduce the incidence of microvascular thrombosis have been used without a clear benefit of one over the other.[1,9] Ketorolac tromethamine is a potent NSAID that provides slightly delayed, but longer lasting analgesia than opiods.[10] Ketorolac also inhibits platelet aggregation via nonspecific inhibition of cyclooxygenase, thereby decreasing the synthesis of prostaglandins, prostacyclins, and thromboxane A2.[11,8] Ketorolac has been shown to be safe in a variety of aesthetic plastic surgery procedures.[11] Still, the drug's presumed association with perioperative bleeding has limited its use in microvascular head and neck procedures due to fear of a recipient site hematoma, which can compress the vascular pedicle, serve as a nidus for infection, and precipitate fistula formation.[9–12,13]

Due to its antiplatelet and analgesic properties, we included ketorolac in our head and neck free flap reconstruction perioperative protocol in 2018. The creation of the protocol allowed for standardization and coordination of services across multiple departments, including plastic surgery, otolaryngology, neurosurgery, and anesthesiology. This study's collection period spanned the

Table 4. Surgical Site Complications

	Standard Group, n (%)	Nonstandard Group, n (%)	Total (%)	*P*
Total	18	6	24	
Hematoma				
Recipient	0 (0)	0 (0)	0 (0)	n/a
Donor	0 (0)	0 (0)	0 (0)	N/A
Seroma				
Recipient	0 (0)	0 (0)	0 (0)	N/A
Donor	2 (11.1)	1 (16.7)	3 (12.5)	1.000
Infection				
Recipient	4 (22.2)	1 (16.7)	5 (20.8)	1.000
Donor	2 (11.1)	1 (16.7)	3 (12.5)	1.000
Wound dehiscence (recipient site)	0 (0)	1 (16.7)	1 (4.2)	0.250
Partial skin graft loss at donor site	2 (11.1)	0 (0)	2 (8.3)	1.000
Partial flap necrosis	0 (0)	2 (33.3)	2 (8.3)	0.054
Total flap necrosis	0 (0)	0 (0)	0 (0)	n/a

time of the protocol's initiation, allowing a comparison of two cohorts. The nonstandard protocol patients were treated before the implementation of this concerted strategy and did not receive ketorolac. Ketorolac has also been safely adopted into ERAS protocols for free flap reconstruction of other body regions, such as autologous breast reconstruction.[14]

Lee et al investigated the effects of ketorolac on lower extremity free tissue reconstruction, concluding that the drug's use was associated with lower rates of thrombogenic flap complications.[15] There were no flap losses in our series, and our data did not reveal a statistically significant protective effect of ketorolac on thrombotic events, although the two patients with partial flap loss did not receive the NSAID.

Previous studies examining the use of ketorolac in head and neck reconstruction have focused on pain control and bleeding at the recipient site. Our results are consistent with that of Schlieffarth et al in showing no significant association between ketorolac use and recipient site bleeding complications.[16] Schlieffarth and colleagues administered 30 mg doses of ketorolac starting postoperative day one, whereas our first dose was 15 mg given intraoperatively at the time of microanastomosis. The lower dose has been shown to be similar in efficacy for postoperative pain relief as the higher dose, but with less potential for systemic morbidity.[17] Unlike the study by Schlieffarth et al, patients in our study who received ketorolac as part of the standardized perioperative protocol did have a significant reduction in opiate use during the first five postoperative days compared with the nonstandard cohort. Our data reveal no significant association with adverse postoperative events when routine ketorolac was used following implementation of a standardized perioperative protocol in our patients.

Table 5. Systemic Complications

	Standard Group, n (%)	Nonstandard Group, n (%)	Total (%)	*P*
Total	18	6	24	
Pneumonia	0 (0)	1 (16.7)	1 (4.2)	0.250
Cardiac arrest	0 (0)	1 (16.7)	1 (4.3)	0.250
Myocardial infarction	0 (0)	1 (16.7)	1 (4.3)	0.250
Acute kidney injury	0 (0)	0 (0)	0 (0)	N/A
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	N/A
Pulmonary embolism	0 (0)	1 (16.7)	0 (0)	0.250
Sepsis	1 (5.8)	0 (0)	1 (4.3)	1.000
30-day mortality	0 (0)	0 (0)	0 (0)	N/A
Disease recurrence	5 (27.8)	3 (50)	8 (33.3)	0.362

Table 6. Opioid Consumption and Length of Stay

	Standard Group	Nonstandard Group	*P*
Total	18	6	
Daily opioid consumption (MME)	10.5	73.6	0.001
LOS (d)	9	19	0.140
ICU LOS (d)	1.5	13.8	0.003

Infection at the recipient site was the most common complication for both our standard and nonstandard perioperative protocol cohorts (22.2% versus 16.7%, respectively; $P = 1.0$). This is likely secondary to the high number of ablations involving an intraoral environment. There were no significant differences in donor site complications between cohorts. Ketorolac in our patients was not associated with significantly increased rate of systemic complications at 30 days postprocedure. Long-term administration of ketorolac may lead to acute kidney injury.[18] As part of our perioperative protocol, ketorolac is administered for the first five days postoperatively, while fluid status and kidney function are closely monitored. There were no instances of acute kidney injury in any of our patients.

A major impetus for implementing our standard perioperative protocol was to streamline perioperative events. Before the protocol, all patients would go from the OR to the ICU for a variable length of time, often only to benefit from the small nursing-to-patient ratio needed for frequent flap monitoring. Following the standard protocol, patients would go to the ICU for a maximum of 48 hours in a step-down capacity if intensive nursing care was all that was required, and was extended as physiology dictated. With this concerted effort to minimize ICU resources, average ICU length of stay was significantly reduced from nearly two weeks to two days.

Furthermore, our study demonstrates the applicability of our protocol and ketorolac use for a wide spectrum of head and neck defects and free flap types, including muscle, fasciocutaneous, perforator, axial, and bone. Our

evidence shows that ketorolac was well-tolerated, both systemically and locally, by our patients who underwent a diverse array of ablative procedures and head and neck free flap reconstructions.

A major limitation of this study is the small sample size possibly reducing the likelihood of detecting a true effect—this is salient in the context of our study given that we saw no statistically significant differences between the standard and nonstandard perioperative protocol cohorts. In addition, our surgeons were not blinded to the use of ketorolac or adherence to a standard protocol. Likewise, our patients were not randomized to be on a standard perioperative protocol or not. Thus, reduction in surgical complications (partial flap necrosis) and certainly improvement in length of stay and opiate consumption can be attributed to a "learning curve" and Hawthorne effect. Despite these shortcomings, our study adds to the growing body of evidence supporting the implementation of standard perioperative protocols for a large variety of free flaps to the head and neck. Our patients also underwent a diverse number of ablative procedures, speaking to the generalizability of our results for a number of inciting pathologies. Larger, randomized-control trials are needed to further assess the efficacy of ketorolac in head and neck free tissue transfer, although our investigation may serve as an important contribution to the limited data currently available on this topic.

CONCLUSIONS

Standardized perioperative protocols in head and neck free flap reconstruction can reduce hospital resource burden by significantly lowering ICU length of stay. The routine use of ketorolac as part of this protocol was not associated with increased local or systemic complications, and contributed to a significantly reduced postoperative opiate consumption. Ketorolac's function as both an antiplatelet and potent parenteral analgesic makes it an appealing choice for inclusion in head and neck free flap ERAS protocols.

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ACKNOWLEDGMENT

Products mentioned in the article are limited to the pharmaceutical ketorolac (Toradol, F. Hoffman – La Roche Ltd, Nutley, N.J.).

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