



The efficacy of nonsteroidal anti-inflammatories in the prevention of heterotopic ossification following elbow trauma surgery

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Background: Heterotopic ossification (HO) is common following surgery for elbow trauma and can have a significant impact on elbow function. The use of nonsteroidal anti-inflammatories (NSAIDs) for HO prophylaxis following total hip arthroplasty is well described, with the gold standard of indomethacin 25 mg tid for 6 weeks. However, there is sparse evidence relating to the elbow joint, particularly after elbow trauma surgery. We aim to investigate the efficacy of NSAIDs in the primary prevention of HO amongst all adult patients undergoing surgery for elbow trauma and identify risk factors for HO formation.

Methods: A search of the Fiona Stanley Hospital electronic theater database for procedures undertaken for elbow trauma from January 2015 to June 2020 was performed. Electronic medical records and radiographs were reviewed to determine the incidence of HO, prescription of NSAIDs, biographical data, and complications.

Results: One hundred and fifty-three patients were identified of which 78 patients received NSAIDs postoperatively, compared to 72 who did not. The prescribing history of the remaining 3 patients was unknown. In the NSAID group, the typical patient was prescribed 3–7 days of NSAIDs. Ten patients received a prophylactic course (4–6 weeks). The incidence of HO was similar in both groups (24% in those taking NSAIDs vs. 21% in those not taking NSAIDs). Of those specifically prescribed a prophylactic course, 50% developed HO and 50% did not. Statistical analysis demonstrated that patients with increased body mass index and high energy injuries were more likely to develop HO. Overall complications were low within the cohort. Only 1 patient, who was prescribed NSAIDs, suffered a fracture nonunion (1.3%).

Conclusion: NSAIDs did not affect the incidence of HO about the elbow following surgery for trauma amongst our cohort. There was no appreciable difference in the rates of HO amongst those prescribed NSAIDs and those who were not. Increased body mass index and high energy trauma were predictive for higher incidence of HO. Risks of NSAID therapy were low, with only 1 (1.3%) patient suffering a nonunion.

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Heterotopic ossification (HO) is common following surgery for elbow trauma and can have a significant impact on elbow function. The incidence of HO may be as high as 30%–37% following surgery for elbow trauma, with functional impact in 20%–21% of patients.^{1,4} Authors have investigated the role of both nonsteroidal anti-inflammatories (NSAIDs) and radiation therapy as prophylaxis. A randomized controlled trial investigating the use of radiation therapy as prophylaxis was terminated early due to an unacceptably high nonunion rate in the treatment group.² NSAID use also has risk, and has been demonstrated to increase the risk of fracture nonunion post elbow surgery.⁹ The use of NSAIDs for HO prophylaxis following total hip arthroplasty is well described, with the

gold standard of indomethacin 25 mg tid for 6 weeks widely accepted.^{7,10–12} However, evidence for NSAID efficacy in elbow trauma patients is lacking.^{5,8} Sun et al found that a course of celecoxib was associated with lower rates of HO recurrence after open arthrolysis for elbow stiffness secondary to HO.¹³ We believe this to be the first cohort study investigating the effect of NSAIDs on the incidence of HO about the elbow following initial surgery for trauma.

Materials and methods

A search of the Fiona Stanley Hospital, Perth, Western Australia theater database for procedures undertaken for elbow trauma between January 2015 and June 2020 was performed. Operation reports were reviewed on a case by case basis to identify the exact surgical procedure. Only procedures involving the elbow joint were included; specifically, intraarticular distal humerus

Institutional review board approval was not required for this retrospective study.

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fractures, proximal radius and ulna fractures, and elbow dislocations. Pediatric patients (<16 years of age) were excluded. One hundred and fifty-three operations were identified. Surgery was performed within 3 weeks of injury. Prescribed NSAIDs included celecoxib, ibuprofen, indomethacin, meloxicam, and naproxen. Course duration varied from 3 days to 6 weeks. Postoperative radiographs were reviewed for each case and notes were reviewed to determine the degree of HO according to the Hastings and Graham classification.³ Radiographic follow-up was variable between 1 and 37 months. Electronic patient records were reviewed to determine prescription of NSAIDs, biographical data, and complications. Sixty-nine patient records were incomplete, leaving 84 complete data sets for analysis by multinomial logistic regression. R packages ggplot2, caret, and nnet were used.^{6,14,15} Six explanatory variables were fitted to the model to predict the incidence of HO with NSAID, gender, and mechanism as categorical variables, and age, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification as continuous variables. Reference level was “no HO.” The model had an accuracy of 80% and a kappa value of 0.375. Findings were statistically significant if the *P* value <.05.

Results

The overall incidence of HO in our cohort was low (34 of 153 patients; 22%). Seventy-eight patients received NSAIDs postoperatively, compared to 72 who did not receive any NSAID. The prescribing history of 3 patients was not able to be determined. The incidence of HO was similar in both groups (24% taking NSAIDs, and 21% in those not taking NSAIDs). There was no significant difference in the severity of HO between the 2 groups (see Table I). Ten of the 153 patients were specifically prescribed a prophylactic course of NSAIDs at the discretion of the treating surgeon. Within this group, 5 patients developed HO (50%) and 5 did not (50%).

The incidence of HO was similar across high and low energy injuries (23% vs. 22%, respectively). High energy injury was defined as a motor vehicle trauma, fall from a bicycle at speed, fall from >1.5 m. Low energy trauma was a fall from standing height or <1.5 m. HO was more common with increasing age, female gender, increasing ASA classification, and with increasing BMI (see Table II). The rate of HO varied widely depending on the type of NSAID prescribed (Table III). Further breakdown for those specifically prescribed prophylactic NSAID is also shown in Table IV.

A multinomial logistic regression model was used to identify risk factors for HO formation. Six factors were identified: prescription of NSAIDs, age, gender, mechanism of injury, ASA, and BMI. This reduced the data set to 84 complete records, primarily because BMI data were missing for 65 patients. The model identified high energy mechanism of injury (*P* = .038) and increased BMI (*P* = .045) as being predictive for HO formation with an accuracy of 80% and kappa value of 0.375 (see Table V). Excluding BMI increased the number of complete data records to 145, although this model was much less accurate than the model including BMI suggesting that BMI plays a significant role in HO risk.

Complications were low within the cohort. Infection rate was 1.3% (2 patients) with both patients returning to theater for removal of metal. Only 1 patient suffered a fracture nonunion. This patient had been prescribed NSAIDs postoperatively, and returned to theater for removal of metal; no further operative procedure was undertaken. There were 4 other patients who had to return to the theater (total of 4.6% of the cohort): 2 for removal of metal for irritation, 1 for removal of over-stuffed radial head prosthesis, and 1 for arthroscopy for loose bodies causing mechanical symptoms.

Table I
HO severity.

HO grade*	NSAIDs (n = 78)	No NSAIDs (n = 72)	<i>P</i> value
1	16 (21%)	11 (15%)	.44
2	3 (3.8%)	4 (5.6%)	.696
3	0	0	-

HO, heterotopic ossification; NSAIDs, nonsteroidal anti-inflammatories.

* Hastings and Grahams classification.

Table II
Incidence of HO by patient characteristic (n = 153).

Characteristic	Total patients	Patients with HO	Incidence (%)
Prescribed NSAIDs			
Yes	78	19	24
No	72	15	21
Prophylactic course*	10	5	50
Age (yr)			
16-65	116	20	17
>65	37	14	38
Gender			
Male	70	12	17
Female	83	22	27
Mechanism of injury			
Low energy	99	23	23
High energy	49	11	22
BMI			
<18.5	0	0	-
18.5-24.9	33	5	15
25-29.9	29	5	17
30-34.9	14	3	21
35-40	7	2	29
40+	5	3	60
ASA class			
1	76	14	18
2	50	12	24
3	26	8	31
4	0	0	-
5	0	0	-

HO, heterotopic ossification; NSAIDs, nonsteroidal anti-inflammatories; BMI, body mass index; ASA, American Society of Anesthesiologists.

* Patients were prescribed a 4-6 week course of NSAIDs.

Discussion

Our results challenge the notion that NSAIDs reduce the incidence of HO about the elbow after surgery for trauma. There was no appreciable difference in the rates of HO amongst those prescribed NSAIDs and those who were not. High energy mechanism of injury and increased BMI were predictive for higher incidence of HO. Risks of NSAID therapy appear low, with only 1.3% patients suffering a nonunion.

A weakness is the retrospective nature without randomization. There was a highly variable range of NSAIDs prescribed and duration of treatment. Amongst the 10 patients specifically prescribed prophylactic NSAIDs, the rate of HO was 50%. We believe there may have been a selection bias with injury severity and the clinical expertise of the treating surgeon leading to the prescription of prophylactic NSAIDs. BMI data were not available for 65 patients (42%), the presence of which may have strengthened the statistical analysis.

The variable and short radiographic follow-up of many patients may be perceived as a weakness. However, in our experience at our center, it is likely that patients experiencing problems in the longer term, including functional limitation due to HO, would have been referred back to the clinic for further assessment, and therefore captured by our analysis.

Table III
Incidence of HO by type of NSAID.

NSAID	No. of patients prescribed	No. of patients who developed HO	Rate of HO (%)	HO grade 1	HO grade 2
Celecoxib	54	11	20	9 (17%)	2 (3.7%)
Ibuprofen	18	5	28	5 (28%)	-
Indomethacin	3	1	33	1 (33%)	-
Naproxen	2	1	50	1 (50%)	-
Meloxicam	1	1	100	-	1 (100%)

HO, heterotopic ossification; NSAID, nonsteroidal anti-inflammatory.

Table IV
Incidence and grade of HO amongst patients prescribed a prophylactic dose of NSAID.

NSAID	No. of patients prescribed	No. of patients who developed HO	Rate of HO (%)	HO grade 1	HO grade 2
Indomethacin	3	1	33	1 (33%)	-
Celecoxib	4	2	50	2 (50%)	-
Naproxen	2	1	50	1 (50%)	-
Meloxicam	1	1	100	-	1 (100%)
Ibuprofen	0	-	-	-	-

HO, heterotopic ossification; NSAID, nonsteroidal anti-inflammatory.

Table V
Risk factors for development of HO (complete patient data sets only, n = 84).

Characteristic	Total patients	Patients with HO	Incidence (%)	P value
Prescribed NSAIDs				
Yes	47	11	23	.689
No	37	7	19	
Prophylactic course*	4	1	25	-
Age (yr)				
16-65	67	13	19	.668
>65	17	5	29	
Gender				
Male	39	8	21	.997
Female	45	10	22	
Mechanism of injury				
Low energy	60	10	17	.038†
High energy	24	8	33	
BMI				
<18.5	0	-	-	.045†
18.5-24.9	32	5	16	
25-29.9	27	5	19	
30-34.9	13	3	23	
35-40	7	2	29	
40+	5	3	60	
ASA class				
1	40	7	18	.582
2	27	6	22	
3	17	5	29	
4	0	-	-	
5	0	-	-	

HO, heterotopic ossification; NSAIDs, nonsteroidal anti-inflammatories; BMI, body mass index; ASA, American Society of Anesthesiologists.

* Patients were prescribed a 4-6 week course of NSAIDs.

† Statistically significant by multinomial logistic regression ($P < .05$), with NSAIDs, gender, and mechanism as categorical variables, and age, BMI, and ASA class as continuous variables; accuracy 80%, kappa 0.375.

A prospective randomized study would appear low risk and give further information as to the effectiveness of NSAIDs for HO prophylaxis following elbow trauma surgery.

Conclusion

Although there is good evidence for indomethacin prophylaxis following surgery about the hip, NSAIDs did not reduce the occurrence of HO following surgery for elbow trauma. Patients with increased BMI and suffering high energy mechanism of trauma are more likely to develop HO. Risk of nonunion is low with NSAID therapy post elbow trauma surgery.

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