Journal of Clinical Anesthesia 49 (2018) 92–100

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

The effect of nonsteroidal anti-inflammatory drugs on bone healing in humans: A qualitative, systematic review

Alain Borgeat[a,*], Christian Ofner[a], Andrea Saporito[b], Mazda Farshad[c], José Aguirre[a]

[a] Department of Anesthesiology, Balgrist University Hospital, Zurich, Switzerland
[b] Service of Anaesthesiology, Bellinzona Regional Hospital, Bellinzona, Switzerland
[c] Spine Surgery, Balgrist University Hospital Zurich, Switzerland

ARTICLE INFO

Keywords:
Postoperative pain
Nonsteroidal anti-inflammatory drugs
Bone healing
Humans

ABSTRACT

Study objective: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in postoperative pain management. While an increasing number of in vitro and animal studies point toward an inhibitory effect of NSAIDs on bone healing process, the few existing retro- and prospective clinical studies present conflicting data.

Design: The aim of this qualitative, systematic review was to investigate the impact of perioperative use of NSAIDs in humans on postoperative fracture/spinal fusion healing compared to other used analgesics measured as fracture nonunion with radiological control.

Patients/interventions: We performed a systematic literature search of the last 38 years using PubMed Embase and the Cochrane Controlled Trials Register including retro- and prospective clinical, human trials assessing the effect of NSAIDs on postoperative fracture/spinal fusion healing when used for perioperative pain management with a radiological follow up to assess eventual nonunion. Due to different study designs, drugs, dosages/exposition times and different methods to assess fracture nonunion, these studies were not pooled for a meta-analysis. A descriptive summary of all studies, level of evidence, study quality and study bias assessment using different scores were used.

Main results: Three prospective randomized controlled studies and thirteen retrospective cohort human studies were identified for a total of 12′895 patients. The overall study quality was low according to Jadad and Oxford Levels of Evidence scores.

Conclusions: Published results of human trials did not show strong evidence that NDAIDs for pain therapy after fracture osteosynthesis or spinal fusion lead to an increased nonunion rate. Reviewed studies present such conflicting data, that no clinical recommendation can be made regarding the appropriate use of NSAIDs in this context. Considering laboratory data of animal, human tissue research and recommendation of clinical reviews, a short perioperative exposition to NSAIDs is most likely not deleterious. However, randomized, controlled studies are warranted to support or refute this hypothesis.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for postoperative pain management. Medical indications include orthopedic conditions, particularly treatment of patients suffering from fracture pain [1]. NSAIDs have been shown to prevent heterotopic ossifications [2] and to allow a significant reduction of opioid needs and their side effects [3], making this class of drugs one of the cornerstone treatment of postoperative pain in this context. However, there is still an ongoing debate about a possible impairment of bone healing associated with the intake of NSAIDs. In vitro studies and animal trials have demonstrated an inhibitory effect of NSAIDs on the bone healing process [4–7]. Retro- and prospective clinical studies have shown conflicting data making the real clinical relevance of NSAIDs on post-surgery fracture healing/spine fusion in humans questionable [8].

Due to the conflicting results comparing laboratory data on either animal or human tissues and clinical studies [9–14], we performed this qualitative systematic review, whose aim was to highlight and analyze the literature discrepancy dealing with this topic. The main issue was to evaluate the evidence of an increased risk of fracture nonunion assessed by radiographic techniques after post-fracture osteosynthesis/spinal fusion in human after any perioperative NSAIDs exposure.

* Corresponding author at: Department of Anesthesiology, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland.
E-mail address: alain.borgeat@balgrist.ch (A. Borgeat).

https://doi.org/10.1016/j.jclinane.2018.06.020
Received 12 February 2018; Received in revised form 29 May 2018; Accepted 8 June 2018
0952-8180/ © 2018 Elsevier Inc. All rights reserved.

2. Patients and methods

2.1. Qualitative systematic review configuration

To avoid different bias the review configuration was performed according to the advices of different experts [15–17] and is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [18] and the Cochrane Handbook for Systematic Reviews of Interventions [19].

3. Literature search

A computerized search of the electronic databases PubMed EMBASE and the Central Register of Controlled Trials (CENTRAL) for papers published between January 1980 and January 2018 was performed. Only studies in the English, German, French and Spanish language were considered. Maximally expanded search terms with Boolean operators for the terms fracture/fusion AND (union OR malunion OR nonunion OR heal OR healing OR pseudoarthrosis OR fracture healing) and (COX-2 inhibitors OR COX-1 inhibitors OR NSAIDs OR non-steroidal anti-inflammatory drugs OR analgesics). Additionally, the following MeSH terms were used: Fracture Healing [MeSH], Fractures, ununited [MeSH], and Fractures, malunited [MeSH]. Moreover, the clinical trials database, ClinicalTrials.gov. was searched. An additional manual search for theme-related review articles and other relevant material was performed to identify other studies in a snow-balling technique. The references from all studies were screened for additional literature. Duplicates were eliminated.

4. Inclusion and exclusion of trials

Systematic review is best performed with randomized controlled trials. However, due to the very low number of RCT, high quality of other trials was included in the present systematic review.

We included only studies on adults and pediatrics with perioperative NSAID exposure and healing bone/pelvis after fracture surgery or spinal fusion. Outcomes of interest were nonunion or pseudoarthrosis and a minimum length of follow up of 3 months for long-bone/pelvis fracture studies and 1 year for spine fusion studies.

In-vitro human or animal studies were excluded as were clinical studies examining prosthesis, bone ingrowth or the inhibition heterotopic ossification. Also studies which did not assess fracture/spinal fusion healing and dentistry studies were excluded. Case series without controls as well as retraced publications were excluded from the analysis.

No restriction was applied to the type, application from dosage and duration of the NSAID involved. The nonunion assessment had to include a radiological technique [20]. Classifications to assess the nonunion [21] were only included if a radiological diagnosis was included. There were no time restrictions for the radiological follow up time point.

These inclusion criteria allowed for inclusion of all clinical studies on humans assessing nonunion in the perioperative setting with exposition to NSAID without additional confusion created by different animal models, experimental laboratory studies or studies of different fields than orthopedics like dentistry.

The summary of study flow according to the PRISMA statement [18] is provided in Fig. 1.

5. Selection of studies and quality assessment

Two reviewers independently assessed each title for inclusion (C.O, J.A.A.), and relevant abstracts were independently evaluated. If doubt existed regarding relevance, the full text article was assessed. Study quality assessment was performed on blinded manuscripts by the same reviewers using the Jadad Score for RCTs [22] (maximum 5 points, < 3 points = low quality study) and the Oxford Levels of Evidence (OCEBM) score (level 1a = best evidence, level 5 = lowest evidence, < level 2c = low quality study) [23].

Both reviewers independently extracted in duplicate relevant information including age, sex, smoking status, bone involved, method of determining NSAID exposure, dose, duration, class and route of NSAID administration, length of follow up, and definition of nonunion or pseudoarthrosis. Any conflicts were resolved by a third independent reviewer (A.B.). The relevant information extracted was divided according to the 3 main topics: long bone studies, spine studies and pediatric studies and presented in the Tables 1–3.

This systematic review was performed in accordance with the PRISMA guidelines [43].

6. Risk of bias

To avoid inclusion bias all study designs allowing a good quality review (RCTs, cohort studies, case control studies and case series with control groups) were included without excluding any due to a prescreening quality score [17]. Two independent reviewers (C.O. and J.A.A.) performed the screening and assessed each title for inclusion, and relevant abstracts were independently evaluated. In the case of any doubt, the full text article was assessed. A third reviewer (A.B.) was asked to resolve possible conflicts. Study quality assessment was performed by both reviewers (Co: and J.A.A.) using the Jadad [22] and the Oxford levels of evidence [23] scores. In case of disagreement the third independent reviewer (A.B.) was involved. Additionally, the risk of bias for the randomized controlled trials was performed with the Cochrane risk of bias tool [44]. The analysis of known risk factors associated with nonunion were described in Tables 1–3.

7. Results

A total number of 249 records were screened; 222 were discarded for various reasons Fig. 1. Thirty-three studies were assessed for eligibility. The 14 studies of interest not included according to exclusion criteria are shown in Supplement 1. Finally, 19 studies met the eligibility criteria and were included in this review Fig. 1.

8. Study characteristics

The characteristics of the included studies are provided in Tables 1–3. As shown, a great heterogeneity exists among the studies. At least 8 different NSAIDs were used, and three studies [29, 30, 32] did not specify the type of NSAID used. Ketorolac was the most commonly drug used in 9 studies [34–38, 41]. Heterogeneity between studies was also noted for age and sex, and not surprisingly due to mix of RCTs and control studies – the sample size ranged from 42 [25] to 9.995 [29]. Even though there was a high variability in the type of surgery, the involved bone types can be generally categorized as either long bones [24, 25, 27, 29–31] or spine [32–38, 41]. The length of drug exposure was 48 h [41] to > 3 months [32]. Four studies [29–31, 37] did not present specific time frame. Great differences in follow up time, drug dosage and outcome measurement were further sources of heterogeneity.

9. Risk of study heterogeneity

For RCT the Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used as displayed in Supplement 2 [44]. The risk of bias is according to this assessment unclear to high.

Moreover, study quality assessment was performed using the Jadad [22] and the Oxford levels of evidence (OCEBM) [23] scores.

Study quality, smoking status, age of patients, length of NSAID exposure, NSAID class and dosage, involved bone, and nonunion definition were identified, a priori, as potential sources of heterogeneity.

Download English Version:

https://daneshyari.com/en/article/8619589

Download Persian Version:

https://daneshyari.com/article/8619589

Daneshyari.com