Table 1: Excluded studies with reasons for exclusion.

|  |  |  |
| --- | --- | --- |
| Study | Study type | Reason for exclusion |
| Adolphson et al.  | Prospective randomized | Outcome did not include union |
| Ding et al.  | Retrospective cohort | Insufficient data.  |
| Hernandez et al.  | Retrospective case-control | NSAID exposure occurred in the year prior to fracture |
| Horn et al.  | Retrospective cohort | Insufficient data  |
| Jeffcoach et al.  | Retrospective cohort | Control cases included complications due to non-union or infection |
| Karunakar et al.  | Prospective randomized | Short-term follow-up. Outcome of non-union not well defined |
| Moed et al.  | Retrospective cohort | Apparent overlap of patient population in an included study by the same authors |
| Table 1. Excluded studies with reasons for exclusion. |

Table 2: Extracted data from included studies. Three studies with zero events in the exposed and non-exposed cohorts were subsequently excluded from the final analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | NSAID cases | NSAID non-cases | Control cases | Control non-cases |
| Bhandari et al. | 9 | 35 | 26 | 122 |
| Bhattacharyya et al. | 33 | 999 | 72 | 8891 |
| Burd et al. | 11 | 61 | 5 | 113 |
| Deguchi et al. | 15 | 12 | 1 | 45 |
| DePeter et al. | 3 | 335 | 8 | 462 |
| Donohue et al. | 6 | 79 | 28 | 215 |
| Giannoudis et al. | 20 | 9 | 12 | 58 |
| Glassman et al. | 29 | 138 | 5 | 116 |
| Kay et al. 2010 | 0 | 169 | 0 | 52 |
| Kay et al. 2011 | 4 | 621 | 1 | 56 |
| Lumawig et al. | 45 | 209 | 0 | 19 |
| Moed et al. | 0 | 20 | 0 | 46 |
| Park et al. | 5 | 25 | 2 | 56 |
| Pradhan et al. | 12 | 216 | 11 | 166 |
| Randelli et al. | 0 | 40 | 0 | 60 |
| Sagi et al. | 18 | 29 | 4 | 17 |
| Schemitsch et al. | 10 | 77 | 96 | 1043 |
| Sucato et al. | 3 | 155 | 5 | 156 |
| Vitale et al. | 3 | 57 | 10 | 138 |
| Table 2. Extracted data from included studies. Three studies with zero events in the exposed and non-exposed cohorts were subsequently excluded from the final analysis.  |

Table 3. Detailed description of the included studies.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Design | No. of patients | Mean age | Percent smokers | Bone involved | NSAID | Dose | Duration | Nonunion diagnosis | Follow-up |
| Bhandari et al. | Retrospective cohort | 192 | 38 | 24% | Tibial shaft | Not specified | Not specified | Not specified | Any surgical procedure <1 yr after initial surgery with the aim to achieve bony union | 1 year |
| Bhattacharyya et al. | Retrospective cohort | 9995 | 77 | Not specified | Humeral shaft fractures | Not specified | Not specified | Minimum 10 days within 90 days of index injury | Medicare code for surgical fixation 90-365 days after date of injury | 12 months |
| Burd et al. | Retrospective cohort | 190 | 38.6 | 27% | Multitrauma patients with acetabular and long-bone fractures. Femur, Tibia, Radius/ulna, humerus | Indomethacin | 25mg TID | 6 wk | Any fracture which required further treatment for failed healing, failure of clinical or radiographic healing after a minimum of three months, or obviously failed osteosythesis.  | 9 months  |
| Deguchi et al. | Retrospective cohort | 73 | 38 | 22% | Elective primary and revision 1 and 2 level instrumented or noninstrumented spinal fusions with autogenous bone graft | Not specified | Not specified | <3 mo | Plain radiographs, flex/ex views, CT after 1 yr follow-up.  | 12 months  |
| DePeter et al. | Retrospective cohort | 808 | 7 (median) | Not specified | Tibia, femur, humerus, scaphoid, and 5th metatarsal fractures.  | Ibuprofen  | Not specified | Not specified | Bone healing complication included: non-union, delayed union and redisplacement. Not defined. Paper included redisplacement as fracture complication, numbers here only include delayed and non-union.  | Not specified |
| Donohue et al. | Retrospective case-control | 328 | 42.2 | 33% | Femoral and tibial shaft fractures | Ketorolac | 30 or 15 mg q6h | Not specified. In patient only | Reoperation for repair of a nonunion | 1 year  |
| Giannoudis et al. | Retrospective case-control | 99 | 37 | 31% | Femoral shaft fractures | Ibuprofen and Diclofenac |   |   | Surgeon diagnosis, surgical revision | 11.5 months mean time to diagnosis |
| Table 3. Detailed description of the included studies. |

Table 3 continued.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Design | No. of patients | Mean age | Percent smokers | Bone involved | NSAID | Dose | Duration | Nonunion diagnosis | Follow-up |
| Glassman et al. | Retrospective cohort | 288 | 43.8 | 49% | Elective instrumented posterior L4 to sacral fusion with autologous bone graft | Ketorolac | 60mg IM then 30mg q6-8h IM prn ± 10mg PO q6h prn | 2 wk max | Fixation failure, CT or surgical exploration | 24 months  |
| Kay et al. | Retrospective cohort | 8.5 | 8.5 |  | Lower extremity osteotomies Femur, tibia, foot, pelvis | Ketorolac | 0.5 mg/kg q6h prn | Not specified. In patient only | Radiographic | 6 months |
| Lumawig et al. | Retrospective cohort | 273 | 60 | 30% | Elective 1 and 2 level PLIF, local autograft. Pedicle screws and mesh cages.  | Diclofenac | 25-300mg or >300mg over 2wk | 2 wk | Fixation failure, lucency, or movement on Flex/ex views at 2 yrs | 24 months  |
| Park et al. | Retrospective cohort | 88 | 52.7 | 17% | Elective 1 and 2 level lumbar PLIF with iliac crest autograft | Ketorolac | 120mg over 3d | 3 days | Plain radiographs. AP/Lat and flex/ext.  | 12 months  |
| Pradhan et al. | Retrospective cohort | 405 | 56.2 | 0% | Elective 1, 2, and 3 level primary posterolateral lumbar fusion w/ pedicle screw fixation | Ketorolac | 30mg IV q6h | 48h | Movement on flex/ex views or CT | 24 months  |
| Sagi et al. | Prospective randomized | 68 | 40.8 | Not specified | Acetabulum | Indomethacin | 1) 75mg QD x3D 2) 75mg QD x1W 3) 75mg QD x 6W | 3D-6W | CT scan | 6 months  |
| Schemitsch et al. | Prospective randomized | 1226 | 39.5 | 33% | Tibia | Not specified | Not specified | Not specified | Radiographic | 1 year |
| Sucato et al. | Retrospective cohort | 319 | 14.3 | 1% | Elective adolescent idiopathic scoliosis deformity correction, posterior spinal fusion and instrumentation with iliac crest bone graft | Ketorolac | 26.7mg divided over 46h, variable PO ibuprofen | 46h | Surgical exploration | 12 months  |
| Vitale et al. | Retrospective cohort | 208 | 13.4 | 0% | Elective scoliosis deformity correction, posterior fusion | Ketorolac | 0.5mg/kg q6h started within 24-28h | 2-3 days | Surgical exploration | 67 months |

Table 3 continued