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HETEROTOPIC OSSIFICATION IN ACETABULAR FRACTURES: SYSTEMATIC REVIEW AND META-ANALYSIS OF PROPHYLAXIS

OSSIFICAÇÃO HETEROTÓPICA NAS FRATURAS DO ACETÁBULO: REVISÃO SISTEMÁTICA E METANÁLISE DA PROFILAXIA

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ABSTRACT

Objective: Heterotopic ossification is defined as the formation of trabecular bone in soft tissues. It is a common complication after surgical treatment of acetabular fractures. However, its prophylaxis and treatment are still controversial. The objective of this research is to evaluate the effectiveness of actions to prevent the development of heterotopic ossification after surgical correction of acetabular fractures. Methods: A systematic review was carried out with research in the databases PubMed/MEDLINE, Embase, LILACS and Cochrane until August 4, 2020, without restrictions on language and year of publication. Only randomized clinical studies carried out in humans without restrictions based on the dosage of treatments, use and duration of prophylaxis were included in this review. Results: Two studies compared the use of radiotherapy and indomethacin and three compared the use of indomethacin with a placebo or non-indomethacin group. The meta-analysis calculations did not indicate statistical differences between radiotherapy versus indomethacin (RR 1.45, IC 95% 0.97 to 2.17, p = 0,55) and indomethacin versus placebo or not indomethacin (RR 0.85, IC 95% 0.68 to 1.06, p = 0,59). Conclusion: There is insufficient evidence to affirm that the use of radiotherapy or indomethacin are effective to prevent the formation of heterotopic ossification after surgery for fractures of the acetabulum. In addition, the number of complications was higher in the indomethacin group when compared to placebo or no intervention. ***Level of Evidence I, Systematic Review.***

Keywords: Bone Fractures. Disease Prevention. Ossification. Heterotopic. Therapeutics. Clinical Trial.

RESUMO

Objetivo: A profilaxia e o tratamento da ossificação heterotópica ainda são controversos. O objetivo desta pesquisa foi avaliar a efetividade das intervenções para prevenir o desenvolvimento da ossificação heterotópica após a fixação cirúrgica das fraturas do acetábulo. Métodos: Foi realizada uma revisão sistemática com pesquisa nas bases de dados PubMed/MEDLINE, Embase, LILACS e Cochrane até 4 de agosto de 2020, sem restrições quanto ao idioma e ano de publicação. Foram incluídos apenas ensaios clínicos randomizados realizados em humanos sem restrições com base na dosagem dos tratamentos, no uso e na duração da profilaxia. Cálculos de metanálise foram realizados utilizando o software Review Manager desenvolvido pela Cochrane. Resultados: Dois estudos compararam o uso de radioterapia e indometacina e três compararam o uso de indometacina com um grupo placebo ou não indometacina. Os cálculos de metanálise não indicaram diferenças estatísticas entre radioterapia versus indometacina (RR 1.45, IC de 95% 0.97 a 2.17, p = 0,55) e indometacina versus placebo ou não indometacina (RR 0.85, IC de 95% 0.68 a 1.06, p = 0,59). Conclusão: Não há evidências suficientes para afirmar que a utilização da radioterapia ou da indometacina é efetiva para prevenir a formação da ossificação heterotópica após cirurgias por fraturas do acetábulo. Além disso, o número de complicações foi maior no grupo indometacina quando comparado ao placebo ou à não intervenção. ***Nível de Evidência I, Revisão Sistemática.***

Descritores: *Fraturas Ósseas. Prevenção. Ossificação Heterotópica. Terapêutica. Ensaio Clínico.*

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INTRODUCTION

Acetabular fractures are injuries that affect young and elderly individuals and commonly result from trauma with high kinetic energy, as in car accidents, falls from height and extreme sporting events.[1] Most of these injuries require open reduction surgery and stable internal fixation, which aim to restore the normal anatomy of the

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The study was conducted at Departamento de Ortopedia e Traumatologia, Universidade Federal de São Paulo, Escola Paulista de Medicina.
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hip.[2] Acetabular fractures have high morbidity due to damage to articular cartilage, and they can lead to future complications such as disabling osteoarthritis, infection, iatrogenic nerve injury, deep vein thrombosis and heterotopic ossification (HO).[1] The latter is a common orthopedic surgery complication, especially when considering the surgical treatment of acetabular fractures, occurring in approximately 40% of operated patients. It can cause limitations to mobility and impair their quality of life.[3-5]

Heterotopic ossification is a pathological process in which an anomalous bone formation occurs in an extra-bone site, including skeletal muscle tissue and other soft tissues such as fascia, tendon, ligament, subcutaneous skin, and any other connective tissue.[4] Current recommendations for the prevention of HO include the application of gentle exercises for maintaining and gaining range of motion, non-steroidal anti-inflammatory drugs (NSAIDs) and external beam radiation, which are mainly used after fractures and arthroplasty of the hip joint.[6,7]

However, it is known that the literature still remains inconclusive as to the definition of the best prophylactic treatment, the recommended dosages and the ideal time for its utilization.[7-10] A systematic review with meta-analysis of observational studies showed no significant difference in the effectiveness of the use of radiation or NSAIDs in the prevention of HO.[9] The authors also noticed that there was a high level of heterogeneity associated with a low quality in the observational studies included in their investigation.[9] Faced with the controversies pointed out in observational studies,[5,9] the aim of this research was to evaluate the effectiveness of interventions to prevent the development of heterotopic ossification after surgical fixation of acetabular fractures investigated in randomized clinical trials.

METHODS

This systematic review was conducted in accordance with the guidelines of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA*[11] and was registered in *International Prospective Register of Systematic Reviews (PROSPERO)*. The registration number is CRD42020202676.

Data sources and studies

A researcher (T.S.P.B) elaborated the search strategies and the electronic search in the databases PubMed / MEDLINE, Embase, LILACS and *Cochrane Central Register of Controlled Trials*. Reference lists of eligible studies were also researched.

To guide the search for scientific publications of intervention studies, a discriminated clinical question was elaborated based on the strategy defined by the acronym PICO.[12] Thus, we determined that: P = persons with acetabular fractures; I = interventions to prevent heterotopic ossification; C = control group or another intervention; and O = expected outcomes, which includes the presence or absence of HO detected by imaging tests. In addition, other outcomes were investigated, with the presence of adverse effects arising from the interventions, the presence or absence of pain, the assessment of range of motion, quality of life and economic impacts.

The search terms were used in combination with the Boolean operators AND and OR, which are presented in Table 1.

Table 1. Search Terms.

1	Acetabulum [MeSH Terms]
2	Fractures, Bone OR Fracture Fixation OR Fracture Healing
3	Ossification, Heterotopic
4	Myositis Ossificans
5	pathologic* OR ectopic or heterotopic
6	extraosseous OR heterotopic OR metaplastic OR para-articular OR paraarticular OR pathologic* OR periarticular
7	myositis OR dystrophic OR ectopic OR heterotopic OR metaplastic OR para-articular OR paraarticular OR pathological OR periarticular
8	myo-osteosis OR neurogenic osteoma OR osseous heteroplasia OR ossifying fibromyopathy OR synostosis
9	3 or 4 or 5 or 6 or 7 or 8
10	1 AND 2 AND 9

The criteria used for inclusion of the papers were: (1) studies conducted in humans; (2) in adults who underwent fixation surgery for acetabular fractures; and (3) randomized or quasi-randomized clinical trials of any preventive intervention for heterotopic ossification after open reduction and internal fixation of acetabular fractures; (4) any preventive method, either local or systemic, for HO after acetabular surgery, compared with non-intervention, placebo intervention, or alternative preventive scheme; (5) no restrictions based on dosage, utilization and duration of prophylaxis; (6) no restrictions on language and publication year. The exclusion criteria were as follows: case reports or narrative review articles, conference abstracts, animal or in vitro experiments, and studies using replacement arthroplasty.

All stages of the screening of articles were carried out using the Rayyan *software*, which enables rapid exploration and filtering of eligible studies.[13] The analysis of titles and abstracts and full reading were carried out by two researchers independently (T.S.P.B and G.P.G), where any disagreements were resolved between the members of the research team. After the studies were read in their entirety, the following information was collected: authors and year of publication, study design, country where the study was conducted, sample size, average age, participants and intervention time, intervention, outcomes and results (presence or absence of HO detected by imaging tests; data on adverse effects; presence of pain and range of motion; quality of life and economic impacts when this information was available in the studies).

Risk of bias and quality evaluation

The risk of bias in the included studies was assessed by two authors independently (T.S.P.B and G.P.G). As recommended by *The Cochrane Collaboration*[14] "risk of bias" tool, the following six methodological domains were evaluated: (1) *Sequence generation,* (2) *Allocation concealment*, (3) *Blinding of participants, personnel and outcome assessors*, (4) *Incomplete outcome data*, (5) *Selective outcome reporting* e (6) *Other sources of bias.* For each domain, a judgment was assigned as follows: "*low risk"* of bias; "*high risk*" of bias; or "*unclear risk*" of bias; the latter reflecting lack of information or uncertainty about the potential for bias. Disagreements between authors regarding the risk of bias for each domain were resolved by consensus.

The quality evaluation of the studies was performed using the *Grading of Recommendations, Assessment, Development, and Evaluations* (GRID).[15,16] The quality of study evidence was classified into four categories: high, moderate, low or very low.[16]

Statistical analysis

We performed the meta-analysis according to the recommendations of the *Cochrane Collaboration*.[17] We used the Review Manager software (RevMan Web).[17] We calculated the *risk ratio* with 95% confidence interval using the random effects model. We examined heterogeneity using statistics I,[2] where a statistic of 75% or more indicates a considerable level of inconsistency between the studies.[14]

Compliance with ethical guidelines

This article is a secondary study based on previously published studies. Therefore, there is no direct involvement of, nor exposure of direct data extracted from, study participants.

RESULTS

The surveys were conducted until August 4, 2020. We identified a total of 215 articles in the databases and an additional article was collected by manual search on *Google Scholar*. Then, we removed 41 duplicates and deleted 156 articles by screening titles and abstracts. We read 18 full articles, of which 13 were excluded: twelve studies had another type of design than a clinical trial,[18-29] and one presented patients from another research published and included in this article.[30] Of the total, five met the inclusion criteria (Figure 1).[31-35]

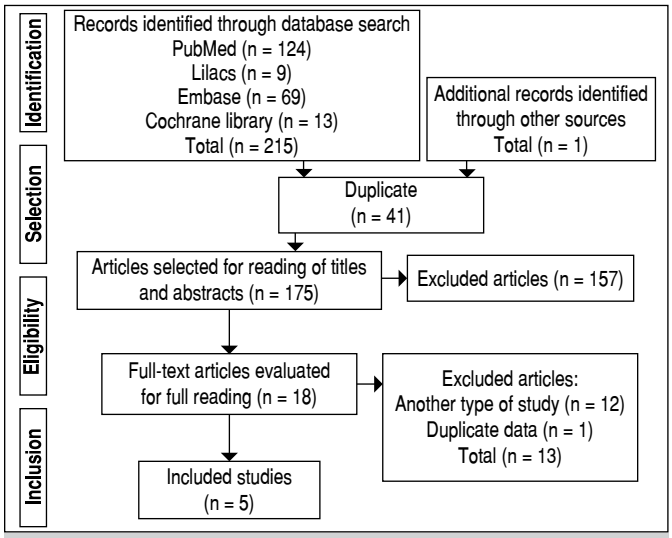

Figure 1. Flowchart of study selection.

The characteristics of the five studies included[31-35] are presented in Table 2 and 3. All studies were classified as randomized clinical trials[31-35] and performed in the United States. A total of 557 participants, including men and women, participated in the studies.

Table 2. Characteristics of the included studies on prevention of heterotopic ossification in patients with acetabular fractures.

Author, year	Type of study	Sample size / gender / average age	Country	Participants and intervention time	Intervention	Comparison or control	Outcome	Results	GRADE Quality of evidence
Burd et al., 2001[31]	Randomized clinical trial.	N = 150 105 M 45 F (Group *Radiation* – average age 44) (Group *Indomethacin* - average 41 years old)	USA	Patients with operative stabilization of acetabular fractures by open reduction and internal fixation. Dose: 800 cGy of local radiation therapy in the hip within seventy-two hours after the operation. Indomethacin (25 mg three times daily) starting within twenty-four hours after surgery for 6 weeks. Duration of follow-up: average thirteen and sixteen months.	*Radiation* (n = 78)	*Indomethacin* (n = 72)	HO classified according to *Brooker** None (grade 0) Mild (grade I and grade II) Severe (grade III and grade IV)	Brooker Grade III or IV heterotopic ossification developed in eight (11%) patients randomized for treatment with indomethacin and three (4%) patients randomized for treatment with radiation therapy. There were no differences between the treatment groups regarding heterotopic ossification (p = 0.22). Local radiation therapy and indomethacin were considered effective prophylaxis against heterotopic ossification after surgical treatment of acetabular fractures.	⊕⊕⊕⊕ DISCHARGE

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Karunakar et al., 2006 [32]	Clinical trial. prospective, randomized double-blind controlled	N = 127 100 M 27 F Indomethacin group: average age 37 years old Placebo group: average age 39 years old	USA	Patients with operative stabilization of acetabular fractures through a subsequent *Kocher-Langenbeck* approach. Dose: 75 mg *Indomethacin* a single daily dose. Intervention time: 6 weeks	*Indomethacin* (*Merck Inc., Whitehouse Station, New Jersey*) Before (n = 63) After (n = 59)	Placebo Before (n = 64) After (n = 62)	HO classified according to *Brooker** None (grade 0) Mild (grade I and grade II) Severe (grade III and grade IV)	Grade III to IV occurred in nine of 59 patients (15.2%) in the indomethacin group and 12 of 62 (19.4%) who received placebo. There is no statistically significant difference between the two groups (chi-square test, p = 0.722). Fisher's exact test showed no significant association between Brooker categories (none, mild, severe) and treatment groups (p = 0.334).	⊕⊕⊕⊕ DISCHARGE
Matta e Siebenrock 1997[33]	Randomized clinical trial.	N = 107 Gender NR Indomethacin group: average age 40,3 years old *Non-indomethacin* group: average *age* 45.7 years old	USA	Patients with acetabular fractures underwent surgery by Kocher-Langenbeck (KL), ilioinguinal (II) or extended iliofemoral approach. Dose: 100 mg per suppository at the end of the operation, then 25 mg orally or rectally. Intervention time: three times a day for six weeks.	*Indomethacin* Before (n = 61) After (n = 57)	*No indomethacin* Before (n = 46) After (n = 44)	HO evaluated by AP radiograph of the pelvis and classified as grade 0 (none), grade 1 (minimum) or grade 2 (moderate to severe) ROM	Of the patients receiving indomethacin, 30 (52.6%) did not develop ossification assessed by simple radiograph compared to 19 (43.2%) in the untreated group. Two patients (1.9%) developed clinically significant ossification (grade 2) with loss of hip motion greater than 20% compared to the non-involved side. Both received indomethacin and the operation was by a KL approach.	⊕⊕⊕ MODERATE

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Author, year	Type of study	Sample size / gender / average age	Country	Participants and intervention time	Intervention	Comparison or control	Outcome	Results	GRADE Quality of evidence
Moore et al., 1998[34]	Clinical trial, prospective, randomized, blind	N = 75 52 men 23 women Indomethacin group: average age 43 years old Radiation group: average age 47 years old	USA	Adult patients who underwent open reduction and internal fixation of acetabular fractures by means of a Kocher-Langenbeck, a combined ilioinguinal and Kocher-Langenbeck, or an extended iliofemoral approach. Dose: 25 mg of *Indomethacin* Intervention time: three times a day for six weeks. Duration of follow-up: 12 months. Radiation with 800 cGy three days after the operation	*Indomethacin* Before (n = 20) After (n = 39)	Radiation therapy Before (n = 46) After (n = 33)	HO evaluated by simple X-rays and classified according to *Brooker** None (grade 0) Mild (grade I and grade II) Severe (grade III and grade IV)	Cochran-Armitage analysis showed no significant difference between the two treatment groups regarding the formation of HO (p = 0.089). Indomethacin and single-dose radiation therapy are safe and effective in preventing HO after the operation of acetabular fractures.	⊕⊕⊕ MODERATE
Sagi et al., 2014[35]	Clinical trial, prospective double-blind randomized	N = 98 70 men 28 women Indomethacin group: average age 43 years old Radiation group: average age 47 years old	USA	Patients who suffered an acetabular fracture underwent open reduction and internal fixation of their acetabular fracture by a Kocher-Langenbeck approach. Dose: 75 mg PO daily. Intervention time: 6 weeks	*Indomethacin* Before Group 1-3 days (n = 24) Group 2 – one week) (n = 25) Group 3 - six weeks (n = 23) After Group 1 - (n = 17) Group 2- (n = 17) Group 3- (n = 13)	Placebo Before (n = 26) After (n = 21)	HO evaluated by simple X-rays and classified according to *Brooker** None (grade 0) Mild (grade I and grade II) Severe (grade III and grade IV) EVA: pain assessment.	A six-week long treatment with indomethacin does not appear to have a therapeutic effect to decrease the formation of HO after acetabular fracture surgery, and appears to increase the incidence of nonunion. A one-week long treatment with indomethacin may be beneficial to decrease the volume of HO formation without increasing the incidence of pseudoarthrosis. Visual analog scales for pain (VASs) were significantly higher for patients with radiographic nonunion (VAS 4 vs. VAS 1, P = 0,002).	⊕⊕⊕ MODERATE

HO: heterotopic ossification.
* Brooker AF, Bowerman JW, Robinson RA, Riley LH Jr. Ectopic ossification following total hip replacement. Incidence and a method of classification. J Bone Joint Surg Am. 1973;55(8):1629-1632.
ROM: range of motion.
AP: Antero-posterior
VAS: Visual analog scale for pain.

Table 3. Characteristics of the included studies on prevention of heterotopic ossification in patients with acetabular fractures.

Summary of findings:

Interventions to prevent heterotopic ossification in patients with acetabular fractures

Patient or population: Patients with surgical stabilization of acetabular fractures
Setting: Hospital
Intervention: Indomethacin
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with [Placebo/ no intervention]	Risk with [Indomethacin]				
Heterotopic ossification assessed with: Placebo versus Indomethacin follow up: average 6 weeks	598 per 1.000	497 per 1.000 (395 to 622)	RR 0.83 (0.66 to 1.04)	256 (3 RCTs)	⊕⊕⊕ MODERATE	No differences were found between the studies regarding the outcome
Range of motion	0 %	20 %	–	101 (1 study)	⊕⊕⊕ MODERATE	Two patients (1.9%) developed clinically significant ossification (grade 2) with loss of hip movement greater than 20% compared with the uninvolved side. The moderate quality of the studies is a result of the small sample size and because there is no available study protocol.
Pain (VAS) in Patients with Nonunion versus Patients with Union	4	1	–	34 (1 studies)	⊕⊕⊕ MODERATE	Pain as reported by VAS was significantly greater in the patients with radiographic nonunion at both the 6-month and 1-year follow-up intervals (P = 0.002). The moderate quality of the studies is a result of the small sample size.

Summary of findings:

Interventions to prevent heterotopic ossification in patients with acetabular fractures

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Setting: Hospital
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Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with [Placebo/ no intervention]	Risk with [Indomethacin]				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias in the included studies

The results of the risk of bias assessment of the included studies are presented in Figures 2 and 3. Although the risk of bias in general was considered low, we identified a high risk of bias in some studies, as shown in Figure 2, because the studies did not meet the following criteria: *sequence generation, allocation concealment, blinding of participants and personnel, selective outcome reporting* and *other bias*.

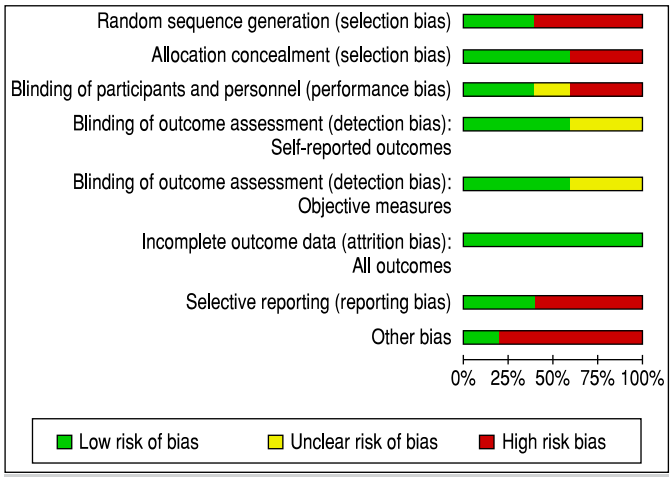

Figure 2. Risk of bias chart

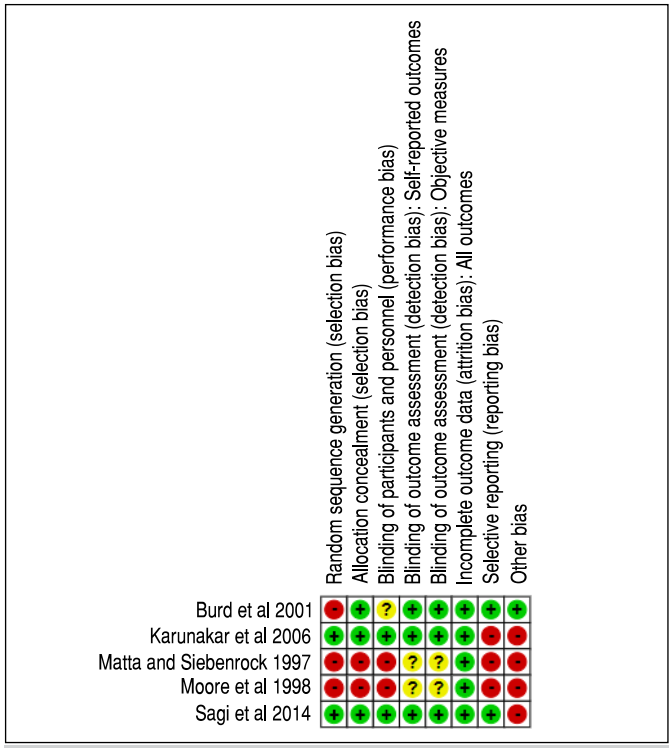

Figure 3. Summary of risk of bias for each trial (the plus sign denotes low risk of bias; the minus sign denotes high risk of bias; the question mark denotes uncertain risk of bias).

Quality evaluation

The individual analysis of the methodological quality of the studies, using the GRADE criteria, showed high quality[31,32] in two studies. In three studies comparing the use of Indomethacin versus Placebo, the GRADE evaluation was grouped according to Table 2. In addition, we present results for the outcome range of motion and pain. The result indicated moderate methodological quality.[33-35] The moderate quality of the studies is a result of the small sample size and because there is no available study protocol.

Intervention and group control or comparison

The interventions for preventing HO in patients with acetabular fractures included: radiotherapy compared to indomethacin (non-steroidal anti-inflammatory drug)[31,34] and the use of indomethacin compared to a placebo group[32,35] or non-indomethacin.[33]

Intervention time and dosages

Indomethacin was used with application of a single daily dose of 75 mg,[32,35] with intervention time of six weeks.[32,35] There was also application of 25 mg of indomethacin[31,34] three times a day for six weeks[31,34] with 100 mg of indomethacin per suppository at the end of the operation, and 25 mg orally or rectally three times a day for six weeks.[33] Moore et al.[34] administered 25 mg indomethacin orally or rectally before the operation and 25 mg three times a day for six weeks. The time and dosage of radiation therapy are described in Table 1.

Presence or absence of pain and range of motion

Only one study reported pain assessment[35] and four studies analyzed range of motion.[31,33-35] The instrument utilized for pain assessment was the Visual Analog Pain Scale.[35] Pain scores were significantly higher for patients who exhibited pseudoarthrosis, diagnosed by radiographic control images at follow-up intervals of 6 months and one year ($p = 0.002$).[35]

About range of motion, data (flexion, extension, internal rotation, external rotation, abduction and adduction) were collected, recorded and compared to the contralateral hip.[35] Joint mobility evaluated by clinical examinations performed at a six-month interval was similar to those performed during the one-year follow-up.[35] Matta and Siebenrock[33] reported that patients with loss of mobility greater than 20% were followed for more than one year. However, this study did not report how many individuals achieved such a loss.[33] In the study by Moore et al.,[34] hip range of motion improved slowly after surgery, but of the total subjects included in this study, 19 patients had a loss greater than 20°. In the study by Burd et al.,[31] the differences in range of motion between the injured side and non-injured side were, on average, 7° in flexion, 9° in external rotation, 8° in internal rotation, and 7° in abduction. Only hip flexion had a significant relationship with the degree of heterotopic ossification ($p = 0.011$), but there was no significant relationship with the treatment group (indomethacin or radiotherapy) ($p = 0.40$).[31]

Quality of life and economic impacts

The studies did not report the impacts of the intervention on quality of life and economic aspects.

Effect of interventions

The results of the interventions to prevent HO in patients with acetabular fractures are presented in Table 1.

Radiation therapy versus indomethacin

Burd et al.[31] concluded that local radiation therapy and indomethacin were effective prophylaxes for preventing heterotopic ossification after surgical treatment of acetabular fractures. However, they found no significant difference in efficacy between the two interventions. Moore et al.[34] reported that the use of indomethacin and single dose radiation therapy are safe and effective in preventing heterotopic ossification after surgical approach for acetabular fractures. However, the authors highlighted that radiation therapy is approximately 200 times more costly than indomethacin therapy.[34] Meta-analysis of randomized clinical trials[31,34] showed no statistical difference in the prevention of HO between radiotherapy and indomethacin (RR 1.45, 95% CI 0.97 to 2.17, $p = 0.07$), and there was no evidence of heterogeneity ($I^2 = 0\%$; $Chi^2 = 0.36$) (Figure 4).

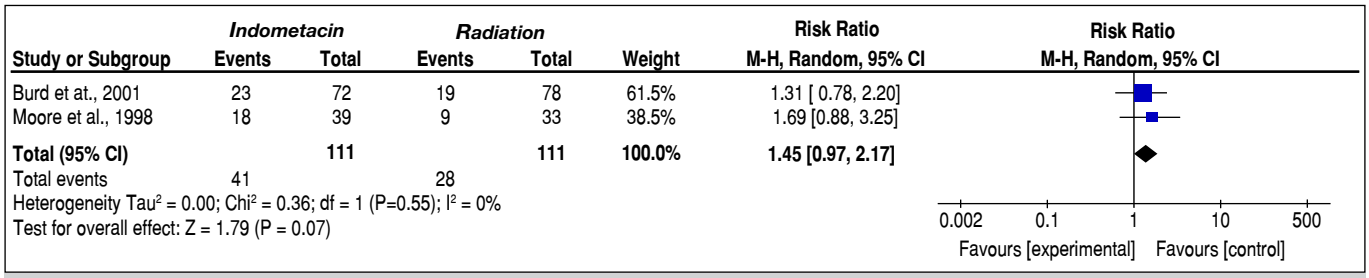

Figure 4. *Forest plot* comparing the risk of heterotopic ossification with radiation therapy and indomethacin.

Indomethacin versus control (placebo or non- intervention)

About the use of indomethacin, two studies reported that this intervention was not effective.[32,33] In addition, Matta and Siebenrock[33] pointed out that the number of patients studied was very small. Karunakar et al.[32] also found no statistical differences in the reduction of the incidence of severe HO with the use of indomethacin compared to the use of placebo. Sagi et al.[35] indicated that using indomethacin for 6 weeks does not appear to have a therapeutic effect to decrease the formation of HO after acetabular fracture fixation surgery. However, they indicated the possibility of increased incidence of pseudoarthrosis associated with this therapy. A one-week long treatment using indomethacin can be beneficial to decrease the volume of HO formation without increasing the incidence of pseudoarthrosis.[35] Meta-analysis of randomized clinical trials[32,33,35] showed no differences for HO results comparing indomethacin with placebo or non-use of indomethacin (RR 0.85, 95% CI 0.68 to 1.06, p = 0.14), and there was no evidence of heterogeneity (I^2 = 0%; Chi^2 = 1.07) (Figure 5).

Adverse effects due to the interventions

Only one study reported increased incidence of pseudoarthrosis.[35] Karunakar et al.[32] reported complications such as deep vein thrombosis, infection in the surgical wound, pseudoarthrosis of the tibia, gastrointestinal bleeding and perforated ulcer in the group that received indomethacin. Six patients who received placebo evolved with deep vein thrombosis and one presented infection of the surgical wound.[32] No complications were reported in the study by Burd et al.[31] No patients using indomethacin had to stop treatment due to gastrointestinal symptoms, although several patients had their treatment stopped by other doctors who did not understand the purpose of the drug. No problems with the healing of surgical wounds were found in patients treated with radiation.[31] Analyzing the complications, meta-analysis[32,35] indicated differences between the indomethacin and placebo groups, indicating statistical evidence that the number of complications was lower in the placebo group (RR 2.04, 95% CI 1.01 to 4.56, p = 0.05). Low heterogeneity was observed between the studies (I^2 = 23%) (Figure 6).

DISCUSSION

This review included five studies involving 557 participants.[31-35] These studies reported on the utilization of radiation therapy and indomethacin for preventing the development of heterotopic ossification after acetabular fractures. The analysis of the studies indicates that the available evidence for the utilization of both radiation therapy and indomethacin, as well as other interventions, is scarce and limited. The evidence on the use of radiation therapy compared to indomethacin, as well as indomethacin compared to placebo, indicated that there were no differences between the interventions. We consider that most studies had a low risk of bias, in addition to moderate and high methodological quality.

A notable finding of this review was the fact that all included studies were conducted in the United States. Another finding concerns the differences found in the studies with regard to the interventions and dosages and intervention time. Certainly, these observations highlight that new interventions should be explored in future studies. In addition,

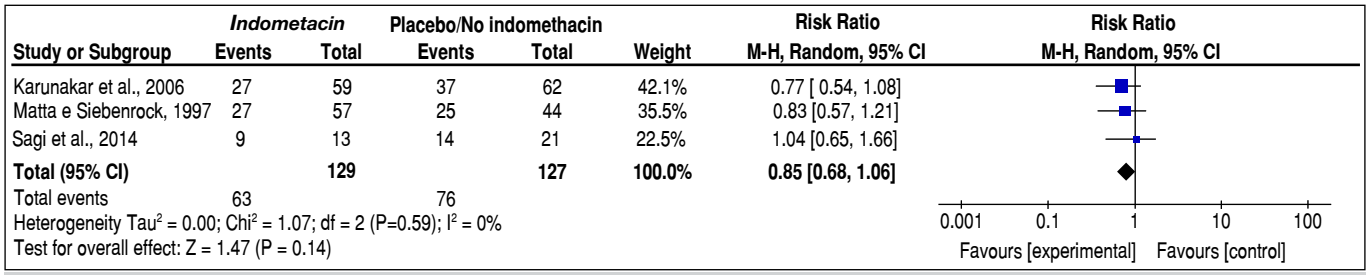

Figure 5. *Forest plot* comparing the risk of heterotopic ossification with radiation therapy and indomethacin.

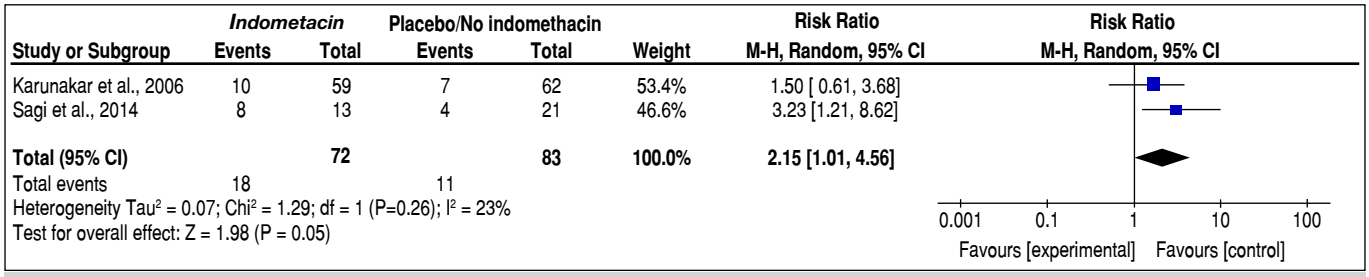

Figure 6. *Forest plot* comparing complications with the use of indomethacin and placebo.

it is important to note that not all studies reported the presence of adverse effects or complications arising from the use of radiation therapy and indomethacin. There were reports of pseudoarthrosis[35] and complications such as deep vein thrombosis, infection in the surgical wound, pseudoarthrosis of the tibia, gastrointestinal bleeding and perforated ulcer when using indomethacin.[32]

Despite the limitation of few published clinical trials on the subject, radiation therapy and indomethacin have been investigated in many observational and longitudinal studies.[18-25] However, we observed that the results of these studies were also contradictory and should be interpreted with caution regarding the benefits and the risks of possible adverse effects, such as the risk of cancer when using radiation therapy and the risk of death from bleeding or gastric perforation, as well as pseudoarthrosis when using indomethacin.[18-25]

As a strength of this review, we highlight the conduct of a comprehensive survey of randomized clinical trials in any language and with no restrictions on year of publication. However, we consider that this systematic review and meta-analysis present some limitations. Firstly, the small number of studies found means that the results of this review cannot be considered definitive. Secondly, considerable heterogeneity was observed by the different comparison methods, dosages and intervention time to prevent the formation of heterotopic ossification. Some interventions were not cited or evaluated as a preventive method, such as the use of corticosteroids and bisphosphonates, suggesting a weakness in the studies performed. In addition, using the GRADE approach (Schunemann 2011), we evaluated the degree of evidence for each outcome reported as moderate in quality. We downgraded the evidence one level because of the risk of bias, reflecting that all five studies presented risk of detection and description of bias. The evidence is not robust for the comparison of indomethacin and placebo found in the evaluation of methodological quality. Therefore, we can state that the numerical results of this review should be interpreted with caution, and require confirmation by future studies with good methodological quality and adequate power.

Therefore, we infer that new randomized and controlled clinical trials need to be conducted to evaluate the effectiveness of the different interventions. Preferably, these studies will have a representative sample size so as to adequately determine the application time and the dosages of the interventions. Robust studies with standardized interventions will be useful to determine changes in clinical practice and to direct future research. Moreover, it is important that future studies analyze the adverse events arising from each intervention and the changes in quality of life, pain control and improvement of the arc of joint motion.

CONCLUSION

In conclusion, there is insufficient evidence to assert that the use of radiation therapy or indomethacin is effective in preventing the formation of heterotopic ossification after acetabular fracture surgery. Also, the number of complications was higher in the indomethacin group when compared to the placebo or non-intervention groups.

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