Radiotherapy and Oncology 116 (2015) 4–9

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Radiotherapy for the prophylaxis of heterotopic ossification: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 24 March 2015
Received in revised form 4 May 2015
Accepted 8 May 2015
Available online 7 July 2015

Keywords:
Heterotopic ossification
Radiotherapy
Randomized controlled trial
Meta-analysis

ABSTRACT

Introduction: Heterotopic ossification (HO) involves the formation of lamellar bone in nonosseous tissue. For HO, radiotherapy has been shown to be an effective prophylactic modality.
Objective: To compare HO outcomes following radiotherapy and to investigate the comparative efficacy of preoperative versus postoperative radiotherapy.
Methods: A systematic search was conducted on Ovid MEDLINE, EMBASE and Cochrane CENTRAL. Studies were included if they were randomized controlled trials (RCTs) that included patients who were prescribed prophylactic radiation for whom relevant HO progression outcomes were reported.
Results: From a literature search of 528 articles, 12 RCTs were included. There was a statistically significant reduction in HO prevalence with multiple as opposed to single fraction radiotherapy ($p = 0.04$), however there was no statistically significant difference when examining HO progression ($p = 0.34$). There was no statistically significant difference in HO progression when comparing a biologically effective radiation dose (BED) of >2500 cGy versus $\leqslant$2500 cGy ($p = 0.28$). As well, no statistically significant difference existed in HO progression between postoperative versus preoperative radiation ($p = 0.43$).
Conclusion: There was no difference between postoperative or preoperative radiotherapy in preventing HO progression. There seems to be no relationship between BED greater or less than 2500 cGy and the efficacy of HO prophylaxis. Multiple fractions seem to be more effective than single fraction radiotherapy in preventing HO progression.
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Heterotopic ossification (HO) is the formation of lamellar bone in non-osseous tissues such as muscles, nerves and connective tissue [1,2]. HO can develop in various sites, including the hip, knee, shoulder and elbow and is usually the result of traumatic acetabular fracture, total hip arthroplasty or central nervous injury [3,4]. The incidence of HO after open reduction of acetabular fractures ranges from 5% to 90% [5].

HO formation is presumed to result from differentiation of pluripotent mesenchymal cells into osteoblasts [6]. Bone morphogenic protein (BMP2) has been shown to induce this process [7]. Specifically, BMP2 interacts with the Wnt/β-catenin in osteoblasts, which leads to differentiation. Differentiation usually occurs 16 h after surgery and peaks at around 32 h postoperatively. It normally takes at least 4–6 weeks for mineralization to be detected by radiographs [6].

The risk factors for developing HO include male gender, osteoarthritis, and previous development of HO at a particular anatomic site [8]. In many cases, HO is asymptomatic and is only detected on imaging. In other cases, it is asymptomatic until it has reached higher degrees of ossification that may affect patients' function [9]. Pain and decreased range of motion are the most common symptoms of advanced HO [10]. To classify the degree of ossification, the Brooker classification system is most commonly employed [11]. The classification is based on AP radiographic views only and is divided into five grades: grade 0, which represents no soft tissue calcification; grade 1, which represents islands of bone within the soft tissue about the hip; grade 2, which represents bone spurs in the pelvis or proximal end of the femur with at least 1 cm between the opposing bone surfaces; grade 3, which represents bone spurs from the pelvis or proximal end of femur with less than 1 cm between opposing bone surfaces; and grade 4, which represents radiographic ankylosis [11].

Two common methods of prophylaxis of HO development are radiotherapy and non-steroidal anti-inflammatory drugs (NSAIDs). In a meta-analysis of randomized controlled trials (RCTs) by Vavken et al., HO outcomes were compared in NSAID vs. radiotherapy treatment arms. In total, 634 patients who received radiation and 661 patients who received NSAIDs were included in the study. There was no significant difference in the

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http://dx.doi.org/10.1016/j.radonc.2015.05.022
0167-8140/

two prophylactic modalities seen (risk ratio (RR) = 1.2; 95% confidence interval (CI) = 0.8–1.8; $p = 0.48$) [12]. However, there is a significant difference between the cost effectiveness of radiotherapy versus NSAIDs [13]. In another meta-analysis by Vavken et al., results strongly supported the conclusion that NSAIDs are considerably more cost effective than radiotherapy [13]. However, compared to NSAIDs, radiation therapy may be associated with lower incidence of grade 3 and 4 HO. Therefore, radiotherapy may be a preferred option in very high risk patients or in patients with contraindications to NSAIDs.

Currently, it is hypothesized that radiation works as a method of prophylaxis by inactivating pluripotent mesenchymal cells before they start differentiating into osteoblasts [14]. Radiation can be either given preoperatively or postoperatively, although the latter remains a more common treatment choice [15,16]. A meta-analysis by Popovic et al. examined the published literature to examine optimal prescription parameters in 5464 patients receiving prophylactic radiotherapy. They found that there was no statistically significant relationship between the percentage of patients receiving HO and radiation dose, and no significant difference in the effectiveness between preoperative versus postoperative radiotherapy [15]. The purpose of our meta-analysis is to determine if these previous findings could be corroborated in a more controlled environment by only considering the results of randomized controlled trials (RCTs). Specifically, our meta-analysis asks whether there is a difference in the development of HO based on fractionation schedule (single vs. multiple), preoperative versus postoperative radiotherapy administration, and high versus low biologically effective radiation dose (BED).

Methods

A systematic literature search on Ovid MEDLINE and Ovid OLDMEDLINE (1946 to February week 4 2015), EMBASE and EMBASE Classic (1947–2015 week 8) and the Cochrane Central Register of Controlled Trials (January 2015) was conducted utilizing the keyword "heterotopic ossification" combined with either "radiotherapy", "radiation prophylaxis", "radiation therapy" or "cancer radiotherapy".

Studies that were included had to be RCTs that contained patients who had all been prescribed a known dose of radiotherapy. The prevalence of HO had to be reported and stratified by radiation site. Studies were only included if the average or median length of radiographic follow-up exceeded eight weeks. Only English trials were included.

Data collection

Collected data included the year of treatment, treatment center, site of radiation, number of treatment sites with radiographic follow-up, radiation dose, timing of radiation (postoperative or preoperative), past history of HO, percentage of sites with any HO prior to study inclusion, percentage of sites developing any HO over the study duration, as well as Brooker grade-specific data for HO prevalence prior to and during the study.

Statistical analysis

Review Manager (RevMan 5.2) by Cochrane IMS was used to conduct the meta-analysis. The Mantel–Haenszel method was applied and a random effects model was used to generate odds ratios (OR) and accompanying 95% confidence intervals (CI). A p-value of $p < 0.05$ was considered statistically significant. The intention-to-treat principle was utilized in all statistical analyses. For the pooled analysis, prevalence rates were used because not all studies included information about baseline HO rates.

Table 1
Baseline demographic data for included randomized controlled trials.

Study (Author, year)	Year of treatment	Treatment center	Site of radiation	Number of Treatment sites with radiographic follow-up	Radiation dose (cGy)/ fractionation	Postoperative versus preoperative radiation	Past patient history of HO	Percentage of sites with any HO previous to study inclusion	Percentage of sites with Brooker grade 1/2 HO previous to study inclusion	Percentage of sites with Brooker grade 3/4 HO previous to study inclusion
Burd (2001)	1992–1999	USA	Hip	78	800/1	Postoperative	Unknown	n/a	n/a	n/a
Hamid (2010)	2005–2008	USA	Elbow	21	700/1	Postoperative	Unknown	n/a	n/a	n/a
Kienapfel (1999)	1992–1993	Germany	Hip	49	600/1	Postoperative	Unknown	n/a	n/a	n/a
Knelles (1997)	1988–1994	Germany	Hip	101	1200/4	Postoperative	Unknown	n/a	n/a	n/a
Knelles 2nd study arm (1997)	1988–1994	Germany	Hip	95	700/1	Postoperative	Unknown	n/a	n/a	n/a
Knelles 3rd study arm (1997)	1988–1994	Germany	Hip	93	500/1	Postoperative	Unknown	n/a	n/a	n/a
Kölbl (1998)	1995–1996	Germany	Hip	46	700/1	Preoperative	Mixed	n/a	n/a	n/a
Moore (1998)	1993–1996	USA	Hip	33	800/1	Postoperative	Unknown	n/a	n/a	n/a
Padgett (2003)	n/a	USA	Hip	29	500/2	Postoperative	Mixed	6/29 = 20.7%	n/a	n/a
Padgett 2nd study arm (2003)	n/a	USA	Hip	30	1000/5	Postoperative	Mixed	7/30 = 23.3%	n/a	n/a
Pellegrini (1992)	1987–1989	USA	Hip	34	800/1	Postoperative	Mixed	12/34 = 35.3%	5/34 = 14.7%	7/34 = 20.6%
Pellegrini 2nd study arm (1992)	1987–1989	USA	Hip	28	1000/2	Postoperative	Mixed	15/28 = 53.6%	5/28 = 17.9%	10/28 = 35.7%
Pellegrini (1996)	1990–1992	USA	Hip	49	800/1	Preoperative	Mixed	15/49 = 30.6%	4/49 = 8.2%	11/49 = 22.4%
Pellegrini 2nd study arm (1996)	1990–1992	USA	Hip	37	800/1	Postoperative	Mixed	8/37 = 21.6%	5/37 = 13.5%	3/37 = 8.1%
Seegenschmiedt (1997)	1992–1995	Germany	Hip	80	700/1	Preoperative	Mixed	54/80 = 67.5%	25/80 = 31.3%	29/80 = 36.3%
Seegenschmiedt 2nd study arm (1997)	1992–1995	Germany	Hip	81	1750/5	Postoperative	Mixed	55/81 = 67.9%	33/81 = 40.7%	22/81 = 27.2%
Seegenschmiedt 3rd study arm (1997)	1987–1992	Germany	Hip	118	1750/5	Postoperative	Mixed	59/118 = 50%	29/118 = 24.6%	30/118 = 25.4%
Seegenschmiedt 4th (1997)	1987–1992	Germany	Hip	131	1000/2	Postoperative	Mixed	66/131 = 50.4%	35/131 = 26.7%	31/131 = 23.7%
Sell (1998)	1992–1993	Germany	Hip	77	990/3	Postoperative	Mixed	6/77 = 7.8%	5/77 = 6.5%	1/77 = 1.3%
Van Leeuwen (1998)	1989–1992	The Netherlands	Hip	43	500/1	Preoperative	Mixed	4/43 = 9.3%	n/a	n/a