Effectiveness of adjunctive analgesics in head and neck cancer patients receiving curative (chemo)radiotherapy: a systematic review

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ABSTRACT

Objective. Our aim was to give an overview of the effectiveness of adjunctive analgesics in HNC patients receiving (chemo)radiotherapy.

Design. Systematic review

Interventions. This systematic review was conducted following the PRISMA guidelines. PubMed, Embase, Web of Science, The Cochrane Library and Clinicaltrials.gov were searched for studies concerning “head neck cancer”, “adjunctive analgesics”, “pain” and “radiotherapy”.

Outcome Measures. Pain outcome, adverse events and toxicity and other reported outcomes e.g. mucositis, quality of life, depression, etc.

Results: Nine studies were included in our synthesis. Most studies were of low quality and had a high risk of bias on several domains of the Cochrane Collaboration tool. Only two studies comprised high quality randomised controlled trials in which pregabalin and a doxepin rinse showed their effectiveness for the treatment of neuropathic pain and pain from oral mucositis respectively in HNC patients receiving (chemo)radiotherapy.

Conclusions. More high quality trials are necessary to provide clear evidence on the effectiveness of adjunctive analgesics in the treatment of HNC (chemo-)radiation induced pain.

Key Words. Adjunctive analgesics; Head and Neck Cancer; (chemo)radiotherapy

INTRODUCTION

The National Cancer Institute defines head and neck cancer (HNC) as "cancer that arises in the head or neck region (the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx)"(1). In Belgium, there were 2,694 new HNC diagnoses in 2016 (2). It is speculated that by 2020, there will be 151,000 new diagnoses in Europe and 833,000 worldwide (3). Treatment modalities for HNC include surgery, radiotherapy, chemotherapy, biotherapy, immunotherapy, targeted therapy and brachytherapy. In most cases, combination therapy has become accepted standard of care (4–6). Multimodal, comprising surgery and/ or radiotherapy often combined with systemic therapy (chemoradiotherapy) are the main treatments for locally advanced HNC (7). However, this treatment may cause severe pain and other complications.

Cancer pain can be classified by cause in three categories: tumour induced pain, iatrogenic pain (induced by treatment) and incidental pain (caused by co-existing conditions) (4). In HNC patients, pain is often a serious complication and is present in a high proportion of patients (4,7–9), before (50%), during (81%) and after treatment (70%) (7). In a meta-analysis performed by Macfarlane et al., pain prevalence in HNC patients was reported to be 57% (95% CI 43% - 70%) before and 42% (95% CI 33% - 50%) after treatment (10). The pain HNC patients experience may be acute pain caused by inflammation of the mucosa (mucositis) and of the skin (dermatitis), or late pain

caused by radiation-induced fibrosis (7). Oral mucositis is one of the most commonly reported adverse events in HNC patients receiving (chemo)radiotherapy. It is known to cause pain that can range from mild to severe and may persist for a period of six months or more after the completion of radiotherapy (6). Post-operative pain (4) and neuropathic pain (11,12) are also often reported. The latter is defined by the International Association for the Study of Pain (IASP) as pain initiated or caused by a primary lesion or dysfunction in the nervous systems, resulting in debilitating pain (13). In case of tumour-related neuropathic pain, tumour infiltration could lead to mixed pain, including nociceptive and neuropathic components. In case of treatment-related neuropathic pain, pain can be considered as pure neuropathic pain and is therefore referred to as purely neuropathic pain (12). Pain may have a substantial impact on the patients' quality of life (QOL) (7) and could lead to social isolation, functional impairment and emotional and spiritual distress (9). Moreover, it could lead to reduced treatment compliance, dose modifications or treatment interruption and in that way, resulting in a lower patient survival (7,9). Therefore, optimal pain control is essential.

Adjunctive analgesics could play an important role in the treatment of neuropathic pain in cancer patients (14). There are different classes of adjunctive analgesics including anticonvulsants, tricyclic antidepressants (TCA), selective serotonin and norepinephrine reuptake inhibitors (SSNRI), N-methyl-D-aspartate (NMDA) receptor antagonists, topical

agents and others (cannabinoids, clonidine, corticosteroids, etc.) (9,11,15). Anticonvulsants include gabapentin and pregabalin and are suggested to help relieve neuropathic cancer pain (9,11,15). Other anticonvulsants investigated are lamotrigine, oxcarbazepine, topiramate, levetiracetam (15). TCAs include amitriptyline, imipramine, clomipramine, doxepin, nortriptyline and desipramine and have been prescribed for years to treat neuropathic pain (11,15). SSNRI, another type of antidepressants, have shown efficacious analgesic effects in the treatment of neuropathic pain and include venlafaxine and duloxetine (9,11,15). Concerning NMDA receptor antagonists, ketamine may be a possible treatment for chronic cancer pain (9,11,15). Cannabinoids also have analgesic properties and could be used for the management of neuropathic cancer pain (9,11,15). Alpha-2 (α-2) adrenergic agonists, such as clonidine and tizanidine, have been used for neuropathic cancer pain, but their specific role has not been established (11,15). Further, corticosteroids, such as dexamethasone and methylprednisolone, could be effective for cancer pain relief (9). Last, local anaesthetics, such as lidocaine and mexiletine, can decrease pain intensity (9,15).

Several reviews have been published on cancer related neuropathic pain, including the recently published review by Edwards et. al (16). However, none of them focuses on the HNC patient population specifically, nor are there any systematic reviews performed. In this systematic review, we give an overview of the effectiveness of adjunctive analgesics in HNC patients receiving (chemo)radiotherapy. This term refers to radiotherapy with curative intent with or without chemotherapy or biotherapy.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews (17). The PRISMA checklist can be found in Appendix A (Supplementary Material). The protocol was registered in the International Prospective Register of Systematic Reviews-PROSPERO (CRD42018085632).

Eligibility criteria

We aimed to identify all types of studies (cohort studies, randomised controlled trials, etc.) that included HNC patients receiving curative (chemo- or bio-) radiotherapy and that investigated the effectiveness of adjunctive analgesics. All articles reporting pain or pain management as outcome, written in English, were included. Papers reporting on pain prevention were excluded.

Literature search method

The following databases were searched: PubMed, Embase, Web of Science and The Cochrane Library. The search terms that were used are listed in Table 1. Clinicaltrials.gov was consulted for ongoing clinical trials. Studies published until February 2019 were included. The search in PubMed was narrowed by filtering studies concerning humans. At the Cochrane Library, the search was limited to title, abstract and keywords. At clinicaltrials.gov, the condition described was “head and neck cancer”, the intervention “pain medication” and “radiotherapy” was completed under the category “other”.

All studies were gathered in a self-constructed database. After removal of duplicates, title and abstract were screened by two individual reviewers (TL and PD). The remaining studies were screened for eligibility by the two reviewers independently. On the selected studies, a snowballing approach was applied: reference lists were screened for additional eligible studies.

Quality assessment

The included studies were subjected to a critical quality assessment, using The Cochrane's Collaboration Tool, by two individual reviewers (TL and LT). Studies were judged by selection, performance, detection, attrition and reporting or other forms of bias (18).

Data extraction

The following data was extracted from the articles: study characteristics (first author, country, article type, drug, comparison, sample size, primary site of disease and chemotherapy received), study therapy characteristics (dose, indication, comparison, number of patients) and outcome (pain outcome, adverse events and toxicity and other reported outcomes e.g. mucositis, quality of life, depression, etc.).

Due to the high heterogeneity in the reported data from the studies, it was impossible to perform a meta-analysis.

RESULTS

Search results

We obtained 264 records from our database search. 216 articles remained present after duplicate removal. After screening on title and abstract, we maintained 74 articles. The main reasons for exclusion were that the articles did not concern adjunctive analgesics or did not concern HNC patients. After full-text screening and quality analysis, nine articles were included for analysis in this review. A list of the excluded articles and the reason for exclusion can be found in Appendix B (Supplementary Material). No additional studies were identified through snowballing (Figure 1).

Study and study therapy characteristics

A summary of the study and study therapy characteristics can be found in Table 2 and 3 respectively. Four studies were performed in the United Stated of America (USA) (19–22), one in China (23), one in Denmark (24), one in France (25), and two in Japan

(13,26). Four studies were randomized trials (13,22–24), two were retrospective cohort studies (19,20), one was a prospective cohort study (25) and two were historically controlled studies (21,26). Four studies investigated the effect of gabapentin (13,19–21), one of pregabalin (23), one of a doxepin rinse (22), one of nortriptyline (24), one of botulinum toxin (25) and one investigated a polymer film containing tetracaine (26). Study medication was indicated for neuropathic pain in one study (23), for painful mucositis in six studies (13,19,20,22,24,26), for pain in general in one study (21) and for radiation induced pain, trismus and masticator spasm in one study (25).

Risk of Bias assessment

The six domains of the Cochrane Collaboration tool for risk of bias were assessed for each of the included studies. A summary of the bias assessment is presented in Figure 2. On the first domain, random sequence generation, four of the nine studies had a low risk whereas five had a high risk of bias. For the next domain, allocation concealment, three studies had a low risk of bias, five had a high risk of bias and for one study, the risk of bias was unclear. There was a high risk of bias for the domain "blinding of participants and personnel" in six studies, a low risk in two studies and an unclear risk in one study. On the domain "blinding of outcome assessment", two studies had a low risk, five had a high risk and two had an unclear risk of bias. In the next domain, incomplete outcome data, a low risk of bias was judged in eight studies and an unclear risk of bias in one

study. On the last domain, selective reporting, eight studies were judged to have a low risk of bias and one to have a high risk of bias. Six studies had a high risk of bias due to a low sample size and the lack of a power calculation. This bias was categorised under "other bias". Three studies did include a power calculation and had an acceptable sample size, resulting into a low risk of bias. The extensive quality assessment can be found in Appendix C (Supplementary Material).

Pain outcomes

Different methods were used to measure the effectiveness of the adjunctive analgesic on pain. Most studies utilised patient reported measures, such as the numeric rating scale (NRS) (23), the Brief Pain Inventory-Short Form (BPI-SF) (23), a visual analogue scale (VAS) (13,24), an 11-point numerical analogue pain scale (22), the Pain Likert Scale (24), the McGill Pain Questionnaire (Danish version) (24), or patient reported pain (not specified) (21,25,26). However, some studies also examined the use (dose and frequency) of pain medications e.g. the use of adjunctive pain medication (19,20), or additional pain medication such as acetaminophen (13), opioids (13,19,20,24), or other analgesics (21,22,24,26). Because of this variety, we could not perform a meta-analysis to obtain an overall result of all studies included. An overview of the reported pain outcomes per treatment type can be found in Table 4 and are described below.

Pregabalin

Jiang et al. (23) conducted a randomized, double-blind, placebo-controlled trial including 64 patients in each group (pregabalin and placebo) and found a decreased pain intensity of 2.44 on the 11-point NRS at week 16 in the pregabalin group compared to the placebo group ($p=0.003$). 19 out of 64 patients receiving pregabalin achieved a pain relief of 50% or more at week 16 compared to only 5 out of 64 patients receiving the placebo ($p=0.003$). Moreover, pain intensity decreased gradually from week 1, but more in the pregabalin group than in the placebo group ($p<0.001$). Further, at week 16, a significantly decreased pain severity, measured by the BPI-SF, was observed in the pregabalin group compared to the placebo group ($p=0.047$).

Gabapentin

Four studies explored the effectiveness of gabapentin in HNC patients receiving radiotherapy (13,19–21) of which two were retrospective cohort studies (19,20), one was a historically controlled study (21) and one comprised a randomised trial (13).

Bar Ad et al. (20) performed a retrospective cohort study in 29 patients and observed that 28 patients used the median dose of gabapentin of 2700 mg/day at week 3, 4, 5 and 6. At week 3 and 4, only 3 of the 29 patients required low doses of narcotics (15-30 mg/day Roxicodone). At week 5 and 6, 10 patients required additional low doses of narcotics (15-40 mg/day Roxicodone).

In a consequent retrospective cohort study in 42 patients, Bar Ad et al. (19) observed that at week 2, 3, 4 and the last week of radiotherapy, 38 patients used gabapentin. Only five patients required an additional median dose of 10 mg/day oxycodone-equivalent at week 2. At week 3, 4, and the last week of radiotherapy, 14 patients required 10 mg/day oxycodone equivalent, 23 patients required 30 mg/day oxycodone equivalent and 30 patients required 60 mg/day oxycodone-equivalent respectively.

Kataoka et al. (13) compared gabapentin plus standard pain control (SPC) to SPC alone in a randomised trial in 20 patients (9 in gabapentin group; 11 in SPC group). They established a non-significant difference in maximum VAS score in the gabapentin group compared to the SPC group (74 vs. 47 resp., $p=0.552$). However, no difference in VAS score was detected between groups at each time point from baseline till week 4. No significant difference was found in the number of days until use of additional analgesics acetaminophen and opioids between groups.

Starmer et al. (21) compared gabapentin (2700 mg/day) to standard treatment (including use of narcotic pain medications) of historical controls in a cohort of 46 patients. They observed significantly lower maximal pain scores in the gabapentin group compared to the control group ($p=0.038$). Moreover, in the gabapentin group, 13% of the patients did not require additional pain medication compared to the control group, in which all patients required narcotics and 70% required multiple narcotics analgesics.

Doxepin rinse

Leenstra et al. (22) compared a doxepin oral rinse to a placebo rinse in a randomised double blinded trial including 140 patients. The area under the curve (AUC) for mean mouth and throat pain reduction was greater in the doxepin group (-9.1) compared to the placebo group (-4.7) ($p<0.001$). The treatment difference after cross-over analysis was -3.5 ($p<0.001$). After 30 minutes, the average mouth and throat pain score reduction was -2.0 in the doxepin group compared to -1.0 in the placebo group ($p=0.0032$). A significant difference in pain reduction was observed 1, 2, 3 and 4 hours after study initiation. No significant differences in use of additional analgesics was found after 2 and 4 hours between groups (8.8% vs. 2.9% and 16.9% vs. 14.5% respectively).

Nortriptyline

Ehrnrooth et al. (24) analysed nortriptyline versus oral morphine in a randomised trial (19 patients in the nortriptyline group, 20 in the morphine group) and found significant lower VAS scores in the opioid group compared to the nortriptyline group 1 and 2 weeks after randomisation (between group difference; p=0.007 and p=0.04 respectively). However, no significant changes in pain were observed within groups from baseline to 1 and 2 weeks post-randomisation. There was a non-significant trend to higher pain scores on the Pain Likert scale in the nortriptyline group compared to the opioid group at baseline and 1 week post-randomisation. According to the McGill Pain Questionnaire, there were no significant differences between groups in sensory, affective or miscellaneous pain at the four time points.

Botulinum toxin

Hartl et al. (25) performed a prospective cohort study to observe the effect of transcutaneous injection of botulinum toxin into the masseter muscles on pain in 19 patients. They found a significant pain improvement after 1 month of botulinum toxin

therapy (p=0.002). However, painful muscle cramps recurred in 11 patients 3.5 months after injection.

Polymer film containing tetracaine

Oguchi et al. (26) used a historically controlled design to compare the effect of a mucosa-adhesive water-soluble polymer film (AD film) containing tetracaine (25 patients) and topical anaesthetics (27 patients). A significantly higher complete pain relief was obtained at rest and while eating in the AD film group compared to the control group (82% vs. 44% and 68% vs. 22% respectively). No significant difference was observed in duration of complete pain relief (30' vs. 30'-2h). Partial and complete pain relief was comparable in both groups. In the AD film group, median duration of grade 3-4 oral pain was 10 days compared to 15 days in the control group. Only 4 patients in the AD film group needed systemic analgesics due to grade 3-4 oral pain compared to 21 patients in the control group.

Reported adverse events and toxicity

An overview of the reported adverse events and toxicities is described below and is summarised in Appendix D (Supplementary Material).

Pregabalin

In the study of Jiang et al. (23), 35 patients (54.7%) in the pregabalin group and 29 patients (45.3%) in the placebo group experienced at least one adverse event (p=0.29). Adverse events described were dizziness, somnolence, facial oedema and increased pain.

Gabapentin

A small number of patients experienced mild side effects or gabapentin related toxicities: 4 patients (13%) in the study of Bar Ad et al. (20), 2 patients (5%) in the other study of Bar Ad et al. (19), 3 of the 9 patients (33%) in the study of Kataoka et al. (13) and 3 of the 23 patients (13%) in the study of Starmer et al. (21). The toxicities

described comprised dizziness, nausea, vomiting, follicular skin rash/ allergic skin reaction, somnolence, vertigo, headaches and fatigue.

Doxepin rinse

In the study of Leenstra et al. (22), stinging and burning, bad taste and drowsiness were reported following the use of the doxepin rinse.

Nortriptyline

Ehrnrooth et al. (24) reported minor side effects in 14 patients in both the nortriptyline (74%) and control group (70%) including nausea, vomiting, constipation, cardial arrhythmia and neurocortical symptoms.

Botulinum toxin

Hartl et al. (25) only reported the injections of the botulinum toxin being painful as toxicity (37%).

Polymer film containing tetracaine

Oguchi et al. (26) did not have any toxicities or side effects to report. There were no acute or chronic adverse effects on the oral mucosa or gastrointestinal tracts, no allergic dermal reactions, no cases of haematological toxicity and no cases of aspiration pneumonia or bronchitis.

Other reported outcomes

The focus of this systematic review was the effect of adjunctive analgesics on pain in HNC patients receiving (chemo)radiotherapy. However, adjunctive analgesics could have other beneficial effects that should be taken into account, such as improvements in

psychological distress, in quality of life (QoL), in radiation induced mucositis, lower depression, better functionality and less cramps, better nutritional management and less weight loss, less secondary infections and a better tumour control and better survival. These are described below and are summarised in Appendix E (Supplementary Material).

Pregabalin

Jiang et al. (23) investigated psychological distress and observed a significant improvement in all subscales of the Profile of Mood States-Short Form (POMS-SF), but not on the Vigor-Activity and Confusion-Bewilderment subscales in the pregabalin group compared to the control group.

Looking at the QoL, significant improvements could be observed in the physiology and psychology domains of the WHO Quality of Life – BREF (WHOQOL-BREF) scores in the pregabalin group compared to placebo ($p=0.004$ and $p=0.01$ respectively).

The Patients Global Impression of Change (PGIC) and the Clinical Global Impression of Change (CGIC) were used to evaluate the improvement and satisfaction of patients with the received treatment. The PGIC scale showed 30 patients (47.6%) who reported treatment success in the pregabalin group, as opposed to 8 patients (12.9%) in the placebo group ($p<0.001$). The CGIC showed 36 patients (57.1%) with treatment success in the pregabalin group, compared to 10 patients (16.1%) in the placebo group ($p<0.001$).

12.5% of the patients in the pregabalin group used rescue medication, while this number was 40.6% in the placebo group ($p<0.001$).

Compliance was comparable in both groups: 80.5% of patients took 80% or more of their prescribed medication.

Gabapentin

Bar Ad et al. examined radiation induced mucositis and radiation induced dysphagia in both studies (19,20). In their first study (20), all patients developed mucositis. Grade 3 mucositis occurred in 6% of the patients and no grade 4 mucositis was reported. 33% of patients did not report any swallowing difficulty. No grade 4 dysphagia was reported.

In their subsequent study (19), all patients developed mucositis. No grade 4 mucositis was reported. No grade 4 dysphagia was reported.

Kataoka et al. (13) also followed up on oral mucositis and reported that all patients experienced oral mucositis. Grade 3 or 4 mucositis occurred in 45.5% of the patients in the control group compared to 63.6% in the gabapentin group.

Concerning QoL, no significant decrease was observed in most domains over 4 weeks of radiotherapy between both groups. Weight gain was significantly higher in the gabapentin group compared to the control group (p=0.0062).

Starmer et al. (27) focussed on percutaneous endoscopic gastrostomy (PEG) use and physiological outcomes. PEG use was introduced later during treatment course and was removed earlier in the gabapentin group compared to the historic control group (PEG introduction: 3.7 vs. 2.29 weeks; PEG removal: p=0.013; 7.29 and 32.56 weeks; p=0.039). 21.7% of patients in the gabapentin group never used their PEG tube compared to 4.3% in the control group (p=0.038). Patients in the gabapentin group lost 7.45% of their initial body weight on average, while this was 11% in the control group (p=0.037). Velopharyngeal closure, tongue base retraction, laryngeal elevation,

epiglottic tilt and pharyngeal constriction were less affected in the gabapentin group. Significantly lower penetration-aspiration scale (PAS) scores were found in the gabapentin group compared to the control group (1.89 vs. 4.0; p=0.052), indicating better airway protection. Significantly higher functional oral intake scale (FOIS) scores were found in the gabapentin group compared to the control group (5.4 vs. 3.21; p=0.0003) indicating more advanced diet levels.

Doxepin rinse

No other outcomes were reported by Leenstra et. al (22).

Nortriptyline

Ehrnrooth et al. (24) used the Beck's Depression Inventory (BDI) to assess the degree of depression. A significant reduction in BDI scores was observed in the nortriptyline group compared to the oral morphine group (p=0.02).

Botulinum toxin

Hartl et al. (25) determined the patients' functionality and muscular cramps and observed a significant improvement in overall functional score ($p=0.04$) and muscular cramps ($p=0.04$) after botulinum toxin injection. There was no significant improvement in jaw opening.

Polymer film containing tetracaine

Oguchi et al. (26) observed mucositis in 88% of the patients in the AD film group compared to 92% in the control group.

17 patients in the AD film group did not require intravenous (IV) infusions or hyperalimentation compared to 9 patients in the control group. In the AD film group, less weight loss and a better weight recovery was observed compared to the control group (not significant).

No secondary bacterial or fungal infection of the oral cavity and/or oropharynx was observed in the AD film group compared to four cases of oral infection and two cases of aspiration pneumonia in the control group.

No significant difference in 3-year local control rate was found between both groups (96% vs. 92%) nor was any difference detected regarding the 3-year disease free survival rate (87% vs 85%).

DISCUSSION

In this systematic review, our aim was to provide an overview of the effectiveness of adjunctive analgesics in HNC patients receiving (chemo)radiotherapy. Out of the 216 articles obtained through our database search, we could select and include nine studies that met the inclusion criteria and were relevant to this topic. Five studies concerned research into anticonvulsants: one in pregabalin (23) and four in gabapentin (13,19–21). The four remaining studies investigated the effect of a doxepin rinse (22), nortriptyline (24), botulinum toxin (25) and a polymer film containing tetracaine (26).

There are some limitations to this systematic review. First, because of the high heterogeneity of parameters reported in the trials, we were not able to perform a meta-analysis to obtain a clear comparison between trials. The included studies used different tools to evaluate pain and other outcomes, making this impossible. Next, two of the included studies (23,25) investigated the effect of the adjunctive analgesic *after* radiotherapy, which is a different approach compared to the other studies investigating the effect *during* radiotherapy. Yet, in our opinion, these studies were valuable to be excluded from our analysis. Last, due to the low quality of most of the included studies, the reliability of the reported outcomes is questionable.

Pregabalin, originally an anticonvulsant, is recommended by multiple guidelines for use in several chronic neuropathic pain conditions, including diabetic neuropathy and postherpetic neuralgia. Jiang et al. demonstrated a significant decrease in pain intensity and severity, improved mood states and a higher QoL in patients treated with pregabalin compared to placebo. Some patients experienced dizziness, somnolence, facial oedema and increased pain, but overall, pregabalin therapy was well tolerated. This was a high quality trial with a low risk of bias on all domains of the Cochrane Collaboration tool, meaning these results are highly reliable (23).

Gabapentin, similar to pregabalin, has been used to treat several neuropathic pain syndromes, including diabetic neuropathy, postherpetic neuralgia, chronic pain, post-operative pain and trigeminal neuralgia. Bar Ad et al. proposed in both included studies that gabapentin could be a promising treatment to avoid or reduce the need for narcotic pain medication in HNC patients receiving radiotherapy (19,20). Furthermore, Starmer et al. demonstrated other positive results of gabapentin: less pain, shorter pain duration and less use of narcotics. PEG use was also introduced later, the PEG tube could be removed earlier and less patients actually used their prophylactically placed PEG tube. Swallowing function was better maintained as well (21). However, these studies had a high risk of bias on several domains of the Cochrane Collaboration tool, due to the low sample size and the design of the studies as it were two retrospective cohort studies and one historically controlled study. Kataoka et al. performed a randomised trial comparing gabapentin to standard treatment. They could not demonstrate a beneficial effect of gabapentin (13). Two domains of the Cochrane Collaboration tool comprised a high risk

of bias and two domains comprised an unclear risk of bias. Therefore, further research is necessary to provide evidence on the effectiveness of gabapentin.

Doxepin hydrochloride is a tricyclic antidepressant and when administered topically, it has anaesthetic and analgesic properties. This doxepin rinse was shown to be statistically significantly superior to a placebo rinse in the treatment of oral mucositis pain caused by HNC radiotherapy. Pain reduction was significantly higher in the treatment group (22). This study comprised a highly qualitative trial with a low risk of bias, therefore contributing to reliable results.

Nortriptyline, also a tricyclic antidepressant, is proved to have analgesic properties. It was shown to provide sufficient pain control in some HNC patients, but opioids generally provided better pain relief. As expected, depression scores were lower in patients receiving nortriptyline compared to patients receiving opioids (24). Despite the randomised trial design of this study, an uncertain risk of bias was present for three domains of the Cochrane Collaboration tool. More trials are necessary to determine the effectiveness of nortriptyline in HNC (chemo-)radiation induced pain. It should be noted that in trials investigating pain outcome, the experimental medication is often compared to morphine, while it would be of more interest to perform a comparison between the experimental medication in combination with morphine versus placebo in combination with morphine instead.

Botulinum toxin has mainly been used for the treatment of muscle stiffness, spasticity and dystonia, but also for various types of neuropathic pain. In a study of Oguchi et al., the injection of botulinum toxin significantly improved pain scores and masticator spasms in HNC patients with radiation induced pain. However, pain recurred in 11 of 19 included patients 3.5 months after injection (25). The study had a high risk of bias on five of the seven domains of the Cochrane Collaboration tool, suggesting more research is needed to prove its usefulness in HNC (chemo-) radiation pain.

A polymer film containing tetracaine was developed to treat acute radiation-induced oral mucositis. It comprised tetracaine, ofloxacine, miconazole, guaiazulene and triacetin. A study of Oguchi et al. proved the usefulness of this polymer film to relieve radiation-induced mucositis pain, to maintain a good nutritional management and to prevent secondary oral infections (26). However, this study had a high risk of bias on almost all domains of the Cochrane Collaboration tool. Moreover, it dates from 1998 and results could be outdated. After more than 20 years, no other recent study was found investigating this polymer film more into detail. Therefore, the actual effectiveness of this polymer film in reducing HNC pain has not been established.

Next to the adjunctive analgesics discussed above, there are many other adjunctive analgesics that have been suggested to be beneficial for cancer pain, including antidepressants e.g. amitriptyline, venlafaxine, duloxetine imipramine, but also NMDA

receptor antagonists e.g. ketamine, or others like cannabinoids (9). However, in our literature search, no evidence was found of the effectiveness of these agents for HNC radiation induced pain. Furthermore, our literature search did not include information about the receipt of herbal medication, which we consider a limitation weakness of the study.

As pain in HNC patients is often caused by radiation induced mucositis, in addition to pain caused by the tumour itself, we also included mouth washes in our search, which may contain adjunctive analgesic agents. However, most mouthwashes are used for the prevention of oral mucositis and not to treat pain. Therefore, no studies with e.g. magic mouthwash were included. We performed a specific search for the use of methylene blue as a mouth wash for intractable oral mucositis-related pain which revealed a study by Roldan et. al. showing reduced opioid requirement in patients using this mouth rinse. However, this study was also not included as it concerned only case series (28). Further research on this topic is needed.

CONCLUSIONS

At the moment, there is only evidence of the effectiveness of pregabalin and a doxepin rinse for the treatment of HNC (chemo)radiation induced pain. We therefore conclude that more research is necessary to provide clear evidence on the effectiveness of other adjunctive analgesics. More randomised trials, using standardised pain scales, would be a great contribution to this research question. Our research team is in the setup of a randomised trial to address this need (clinicaltrial.gov: NCT03747562).

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CONFLICT OF INTEREST:

The authors have no conflict of interest to declare.

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