The place and importance of hyaluronic acid in radiotherapy side effects

Místo a důležitost kyseliny hyaluronové při nežádoucích účincích radioterapie

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Summary

Background: Hyaluronic acid (HA) is one of the largest and most important components of the extracellular matrix. It is found in high amounts in the vitreous humor, umbilical cord, dermis, synovial fluid and heart valves. Up to 80–90% of the circulating HA undergoes catabolism in the liver and 10% is eliminated by the kidney. It is widely used in many branches of medicine. Studies have demonstrated that it provides angiogenic and anti-adhesive effect, collagen storage, cell-cell and cell-matrix interactions, balancing osmotic pressure, removing waste, balancing the distribution of high molecular weight proteins and increasing angiogenesis; it has inflammatory effect, provides wound healing and immunostimulators. Along with its basic features, it can undertake different tasks according to the tissue it is in and the cell type it is secreted from. Neither contraindications nor interactions with drugs have been reported to date. When the literature is reviewed, HA appears to be an effective and safe option in the treatment of acute and chronic side effects that will occur or occur due to radiotherapy. However, there is a need for researches on how HA can be used and how long it can be used. ***Purpose:*** In this review, the data about whether HA is effective in reducing acute and chronic side effects caused by radiotherapy were discussed in the light of the literature.

Key words

hyaluronic acid – radiotherapy – side effects

Souhrn

Východiska: Kyselina hyaluronová (HA) je jednou z největších a nejdůležitějších složek extracelulární matrix. Ve větším množství se nachází ve vitreální tekutině, pupeční šňůře, dermis, synoviální tekutině a srdečních chlopních. Až 80–90 % cirkulující HA podléhá katabolizmu v játrech a 10 % je vylučováno ledvinami. Používá se v mnoha oborech medicíny. Studie prokázaly, že má angiogenní a antiadhezivní účinek, působí při ukládání kolagenu, mezibuněčných interakcích a interakcích buněk s buněčnou matrix, vyrovnání osmotického tlaku, odstraňování buněčného odpadu, vyrovnává distribuci proteinů o vysoké molekulové hmotnosti, má zánětlivý účinek, zvyšuje angiogenezi, hojení ran a má imunostimulační účinek. Kromě těchto základních vlastností má řadu dalších funkcí podle typu tkáně, ve které se nachází, a typu buněk, ze kterých je secernována. Dosud nebyly hlášeny nežádoucí účinky ani interakce s léčivy. Podle literatury se HA jeví jako účinná a bezpečná volba při léčbě akutních i chronických nežádoucích účinků, které se vyskytují nebo vyskytnou během radioterapie. Jsou ale třeba další studie zaměřené na to, jakým způsobem a jak často se může HA používat. ***Cíl:*** V tomto přehledném článku jsou ve světle literatury diskutována data týkající se účinnosti HA při snižování akutních a chronických nežádoucích účinků vyvolaných radioterapií.

Klíčová slova

kyselina hyaluronová – radioterapie – nežádoucí účinky

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Introduction

Hyaluronic acid (HA) is a linear polysaccharide chain consisting of repeating glucuronic acid and acetyl-glucosamine disaccharides. It is also known as hyaluronate or hyaluronan. It is produced by enzymes, a type of specialized membrane protein located inside the cell membrane. It is one of the largest and most important components of the extracellular matrix. Mesenchymal cells are the most important cells involved in the synthesis of HA. It is synthesized by almost all cells in the body. It is found in high amounts in vitreous humor, umbilical cord, dermis, synovial fluid and heart valves. Its lowest concentration is in the blood serum and lymph circulation [1–5]. An adult with an average weight of 70 kg has approximately 15 g of HA in the body [6].

It was first isolated from the glassy liquid of cow's eye by Karl Meyer and John Palmer in 1934. HA can be obtained directly from animal sources or bacteria. Animal sources from which it is obtained are cockscomb, umbilical cord, vitreous humor, skin and tendon. The most commonly used source is the cocks, due to its high amount of HA compared to other animal sources. HA obtained from microorganisms through fermentation is of high purity. Its molecular size depends on the source from which it is obtained [2,5,6]. Commercially, there are HA with three different molecular weights. These are called high molecular weight (10,000 kDa), medium molecular weight (500–800 kDa) and low molecular weight (160–240 kDa) HA. By making some changes in the molecular structure of HA, its derivatives that are more resistant both mechanically and chemically were obtained without changing its compatibility and degradable properties in the biological environment [7].

The half-life of HA differs in each organ. While the half-life in circulation is between 2–5 min, it is stated as 1–2 days in the dermis and 1–2 weeks in the cartilage tissue. The HA half-life increases in conditions such as severe blood loss, septicemia, severe burns and major surgery. The vast majority is eliminated through the lymphatic way. Up to 80–90% of the circulating HA undergoes catabolism in the liver and 10% is eliminated in the kidney [6]. Today, it is widely used in many branches of medicine such as orthopedics, dermatology, plastic surgery and cardiovascular surgery. Neither contraindications nor interactions with drugs have been reported to date [5,8].

In this review, the data about whether HA is effective in reducing acute and chronic side effects caused by radiotherapy were discussed in the light of the literature.

The function of hyaluronic acid in the organism

HA has a high water binding capacity. Water retention, which is important for all healing processes, is very high in hyaluronic acid. It provides stability and elasticity in the intercellular space under normal physiological conditions. It plays an active role with fibrin in all steps of recovery at the time of injury [9]. It reduces inflammation by neutralizing free oxygen radicals in the wound area. HA contributes to the migration and differentiation of mesenchymal and epithelial cells. Thus, it accelerates tissue repair by increasing collagen storage and angiogenesis [10]. It reduces the risk of infection by preventing bacterial adhesion with its anti-adhesive properties [8]. The abundance of HA in fetal wounds plays a role in scar-free healing by providing a highly organized cellular structure and matrix. It has angiogenic, inflammatory and immunostimulating properties. In this way, it has been described that the body is a warning system [11–14]. It is also involved in ensuring cell-cell and cell-matrix interactions, balancing osmotic pressure, removing waste and balancing the distribution of high molecular weight proteins. Along with its basic features, it can undertake different tasks depending on the tissue it is found in and the cell type it is secreted from [8–14].

Clinical use of hyaluronic acid

Today, it has become a biomedical product used in different fields of medicine such as orthopedics, dermatology, cardiovascular surgery and cancer diagnosis [5]. Due to its success in preventing scar tissue, it is subject to both clinical and experimental studies. In fetal wounds, wounds heal without scar due to high HA in the fetus [15]. In the study conducted, it was reported that eye drops containing HA applied after cataract operations accelerated tissue repair [12]. It has been observed that the locally used form penetrates into the epithelial tissue, accelerating keratinocyte proliferation and moisturizing the skin by increasing the amount of retinoic acid. In addition, its injection as a cosmetic filler (thickening of the lips, filling of facial wrinkles or soft tissue depressions) received FDA approval in 2003 [14]. It also creates a physical barrier, reducing the adhesion between the nerve and the surrounding tissue [16,17].

Use of HA in radiotherapy

There is quite a limited number of studies on the application of this biomaterial, which is frequently preferred in many fields due to its multifunctional structure listed above, in the field of radiotherapy (RT). Studies have generally focused on patients with breast cancer and prostate cancer. Very few are related to gynecological cancer and head and neck cancer. The mechanism of action on RT is based on the decreasing lymphocyte migration and proliferation, and inhibiting the phagocytosis of granulocytes and macrophage movements [18–22].

Studies conducted on patients with breast cancer receiving RT have generally examined the effect of HA on radiodermatitis. Its effect on acute and chronic adverse reactions has been studied. In the study of Struik et al, they applied HA together with a brachytherapy catheter in patients with early stage breast cancer who will undergo accelerated partial breast radiation. They stated that HA reduced pain, redness, skin/subcutaneous hardening, surgical site infection, pigmentation and radiation dermatitis. As a result, HA was reported to reduce late skin toxicity in patients who underwent chest brachytherapy or robotic surgery [23]. In the study conducted by Primavera et al, it was stated that HA (MAS065D (Xclair)) used 3-times a day in dermatitis caused by radiation in breast cancer patients is effective in im-

proving the skin appearance, erythema and side effects seen in skin hydration, apart from pain and itching [24]. In a prospective study, lotion, which is a mixture of 3% urea, polidocanol and hyaluronic acid, has been used in a standard regimen or intensively from the beginning of RT or on the onset of the symptoms in dermatitis due to RT for breast cancer. It was stated that the recovery rate of radiodermatitis was lower in the standard group [25]. Generally, there are studies showing that HA is beneficial, and there are also studies showing its negative effect. Pinnix et al compared HA and petrolatum gel in patients who underwent RT after breast conserving surgery and developed grade 2 dermatitis. They stated that topically applied HA gel increased the severity of radiodermatitis and was not effective [26].

Studies on the acute and chronic effects of HA in different RT techniques and doses have been conducted in patients with prostate cancer. It has been stated that it has positive effects according to the results of the studies. Gacci et al reported that HA and chondrotin sulfate applied to the bladder in patients receiving RT for prostate cancer are effective in the treatment of radiation-induced cystitis or bladder pain syndrome [27]. In a phase II study, HA gel was injected with fiducialin transrectal implantation between the rectum and prostate in 30 patients with low or moderate risk prostate cancer who were scheduled for hypofractionated RT. They reported that there was no complication related to HA and rectal toxicity caused by RT decreased [28]. In another phase II study, it was stated that HA injection into the rectal wall was effective in reducing acute genitourinary toxicity in patients with prostate cancer undergoing hypofractionated RT [29]. In another study similar to this, it was reported that HA applied to perirectal adipose tissue in patients who underwent intensity modulated brachytherapy or external beam radiation therapy due to prostate cancer was effective in preventing adverse effects related to RT without any side effects [30]. Moreover, Chapet et al reported that even if the dose of HA applied to the rectal wall is increased in patients undergoing stereotactic body radiation therapy due to prostate cancer, there was no increase in the rectal dose. They reported that this meant that acute and chronic toxicity would decrease significantly [31]. In the study of Wider et al, it was stated that HA reduces the side effects related to treatment in patients with prostate cancer who underwent brachytherapy, thus providing an improvement in the quality of life [32]. It has also been reported that it reduces rectal bleeding and mucosal damage in patients who are administered low-dose and high-dose brachytherapy [33,34].

When looking at the studies on other tumors, it is seen that it is generally written on head-neck and gynecological tumors. Preastan et al applied HA gel (once a day for 20 days) in the patient who received RT with cetuximab due to squamous cell carcinoma of the base of the tongue. They reported that HA reduced pain, ulceration, infection and swelling and increased the quality of life [20]. In another case report, it was stated that the large-particle HA gel was effective in the treatment of dry eye caused by RT [35]. In the clinical study conducted by Wu et al, it was reported that erythema and dry desquamation decreased in patients who were applied subcutaneous HA immediately after interstitial brachytherapy due to parotid gland tumor [36]. In the treatment of oral mucositis caused by RT, it has been reported that there is no difference in reducing pain and correcting eating and drinking disorders when HA and standard treatment meet [37].

It has been reported that HA in genitourinary system cancers increases the quality of life in patients. Dinicola et al reported that HA protects and prevents acute (itching, bleeding, burning, and inflammation in the vaginal mucosa) and chronic (fibrosis, inflammation in the vaginal mucosa) side effects in patients who received pelvic RT and brachytherapy for cervical cancer [18]. In another randomized clinical study, patients who received RT for cervical cancer were divided into two groups. Low molecular weight HA vaginal suppositories were used in one group from the beginning of the treatment. It was reported that vaginal dryness, dysparuni, and vaginal inflammation were less common in the group using HA ($P < 0.001$). As a result, they reported that HA allows uninterrupted completion of RT and improves the quality of life [22]. In the study conducted by Murakami et al, HA gel injection was applied to the vesicovaginal septum in patients in whom high-dose brachytherapy was planned for cervical cancer. They reported that hematuria, bleeding, bladder wall injury or urethral injury decreased in patients due to the lowering of the dose of radiotherapy in the bladder [38]. Shao et al compared patients who received hyperbaric oxygen therapy and intravesical HA in the treatment of radiation-induced hemorrhagic cystitis. They reported that both treatments reduced bladder bleeding, pelvic pain and urination frequency in patients they followed for 18 months [21]. In a randomized double-blind study by Ligura et al, they used HA cream to prevent acute skin re-reactions in patients with head-neck, pelvic and breast cancer. They stated that HA reduced the incidence and severity of acute radiation dermatitis [39]. In the review written by Cosentino and Piro, they looked at the efficacy and reliability of HA in the side effects caused by radiotherapy in the vagina and rectal mucosa in patients who received pelvic RT and stated that HA improved the patient's quality of life by reducing radiation-induced inflammation [19].

Conclusion

As a result, it is an accepted view in the literature that HA is an effective method in the treatment of side effects caused by RT. While this agent is preferred, it seems to be an important factor in its preference for treatment in criteria such as its easy availability, non-toxicity to other tissues with its dosage and application method, radioprotective properties by preventing fibrosis and adhesion, preventing inflammation by reducing the immune response and minimizing scar tissue and low cost. It appears that evidence-based data on its current effectiveness are actually lacking. Comparative studies with other treatment meth-

ods are limited. Studies investigating its use in radiotherapy related side effects are needed.

References

1. Ahmadian E, Dizaj SM, Eftekhari A et al. The potential applications of hyaluronic acid hydrogels in biomedicine. Drug Res (Stuttg). 2020; 70(1): 6–11. doi: 10.1055/a-0991-7585.

2. Zhu J, Tang X, Jia Y et al. Applications and delivery mechanisms of hyaluronic acid used for topical/transdermal delivery – a review. Int J Pharm 2020; 578: 119127. doi: 10.1016/j.ijpharm.2020.119127.

3. Walker K, Basehore BM, Goyal A et al. Hyaluronic acid. Treasure Island (FL): StatPearls Publishing 2020.

4. Kim JH, Moon MJ, Kim DY et al. Hyaluronic acid-based nanomaterials for cancer therapy. Polymers (Basel) 2018; 10(10): 1133. doi: 10.3390/polym10101133.

5. Huynh A, Priefer R. Hyaluronic acid applications in ophthalmology, rheumatology, and dermatology. Carbohydr Res 2020; 489: 107950. doi: 10.1016/j.carres.2020.107950.

6. Stern R. Hyaluronan catabolism: a new metabolic pathway. Eur J Cell Biol 2004; 83(7): 317–325. doi: 10.1078/0171-9335-00392.

7. Brown MB, Jones SA. Hyaluronic acid: a unique topical vehicle for the localized delivery of drugs to the skin. J Eur Acad Dermatol Venereol 2005; 19(3): 308–318. doi: 10.1111/j.1468-3083.2004.01180.x.

8. Necas J, Bartosikova, Brauner P et al. Hyaluronic acid (hyaluronan): a review. Veterinarni Medicina 2008; 53(8): 397–411.

9. Abatangelo G, Vindigni V, Avruscio G et al. Hyaluronic acid: redefining its role. Cells 2020; 9(7): 1743. doi: 10.3390/cells9071743.

10. Lloyd L, Kennedy JF, Methacanon M et al. Carbohydrate polymers as wound management aids. Carbohydrate Polymers 1998; 37(3): 315–322.

11. Hiro D, Ito A, Matsuta K et al. Hyaluronic acid is an endogenous inducer of interleukin-1 production by human monocytes and rabbit macrophages. Biochem Biophys Res Commun 1986; 140(2): 715–722. doi: 10.1016/0006-291x(86)90790-4.

12. Vigetti D, Karousou E, Viola M et al. Hyaluronan: biosynthesis and signaling. Biochim Biophys Acta 2014; 2(1): 2452–2459. doi: 10.1016/j.bbagen.2014.02.001.

13. Goldberg RL, Toole BP. Hyaluronate inhibition of cell proliferation. Arthritis Rheum 1987; 30(7): 769–778. doi: 10.1002/art.1780300707.

14. Ariyoshi W, Okinaga T, Knudson W et al. High molecular weight hyaluronic acid regulates osteoclast formation by inhibiting receptor activator of NF-kB ligand through Rho kinase. Osteoarthritis Cartilage 2014; 22(1): 111–120. doi: 10.1016/j.joca.2013.10.013.

15. Lovvorn HN, Cass DL, Sylvester KG et al. Hyaluronan receptor expression increases in fetal excisional skin wounds and correlates with fibroplasia. J Pediatr Surg 1998; 33(7): 1062–1069. doi: 10.1016/s0022-3468(98)90532-2.

16. Dam-Hieu P, Lacroix C, Said G et al. Reduction of postoperative perineural adhesions by Hyaloglide gel: an experimental study in the rat sciatic nerve. Neurosurgery 2005; 56 (2 Suppl): 425–433; doi: 10.1227/01.neu.0000156845.41626.e9.

17. Ikeda K, Yamauchi D, Osamura N et al. Hyaluronic acid prevents peripheral nerve adhesion. Br J Plast Surg 2003; 56(4): 342–347. doi: 10.1016/s0007-1226(03)00197-8.

18. Dinicola S, Pasta V, Costantino D et al. Hyaluronic acid and vitamins are effective in reducing vaginal atrophy in women receiving radiotherapy. Minerva Ginecol 2015; 67(6): 523–531.

19. Cosentino D, Piro F. Hyaluronic acid for treatment of the radiation therapy side effects: a systematic review. Eur Rev Med Pharmacol Sci 2018; 22(21):7562–7572. doi: 10.26355/eurrev_201811_16298.

20. Presta G, Puliatti A, Bonetti L et al. Effectiveness of hyaluronic acid gel (Jalosome soothing gel) for the treatment of radiodermatitis in a patient receiving head and neck radiotherapyassociated with cetuximab: a case report and review. Int Wound J 2019; 16(6): 1433–1439. doi: 10.1111/iwj.13210.

21. Shao Y, Lu GL, Shen ZJ.Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int 2012; 109(5): 691–694. doi: 10.1111/j.1464-410X.2011.10550.x.

22. Delia P, Sansotta G, Pontoriero A et al. Clinical evaluation of low-molecular-weight hyaluronic acid-based treatment on onset of acute side effects in women receiving adjuvant radiotherapy after cervical surgery: a randomized clinical trial. Oncol Res Treat 2019; 42(4): 217–223. doi: 10.1159/000496036.

23. Struik GM, Godart J, Verduijn GM et al. A randomized controlled trial testing a hyaluronic acid spacer injection for skin toxicity reduction of brachytherapy accelerated partial breast irradiation (APBI): a study protocol. Trials 2018; 19(1): 689. doi: 10.1186/s13063-018-3035-3.

24. Primavera G, Carrera M, Berardesca E et al. A double-blind, vehicle-controlled clinical study to evaluate the efficacy of MAS065D (XClair), a hyaluronic acid-based formulation, in the management of radiation-induced dermatitis. Cutan Ocul Toxicol 2006; 25(3): 165–171. doi: 10.1080/15569520600860009.

25. Pardo Masferrer J, Murcia Mejía M, Vidal Fernández M et al. Prophylaxis with a cream containing urea reduces the incidence and severity of radio-induced dermatitis. Clin Transl Oncol 2010; 12(1): 43–48. doi: 10.1007/s12094-010-0465-0.

26. Pinnix C, Perkins GH, Strom EA et al. Topical hyaluronic acid vs. standard of care for the prevention of radiation dermatitis after adjuvant radiotherapy for breast cancer: single-blind randomized phase III clinical trial. Int J Radiat Oncol Biol Phys 2012; 83(4): 1089–1094. doi: 10.1016/j.ijrobp.2011.09.021.

27. Gacci M, Saleh O, Giannessi C et al. Bladder instillation therapy with hyaluronic acid and chondroitin sulfate improves symptoms of postradiation cystitis: prospective pilot study. Clin Genitourin Cancer 2016; 14(5): 444–449. doi: 10.1016/j.clgc.2016.01.016.

28. Boissier R, Udrescu C, Rebillard X et al.Technique of injection of hyaluronic acid as a prostatic spacer and fiducials before hypofractionated external beam radiotherapy for prostate cancer. Urology 2017; 99: 265–269. doi: 10.1016/j.urology.2016.09.045.

29. Chapet O, Decullier E, Bin S et al. Prostate hypofractionated radiation therapy with injection of hyaluronic acid: acute toxicities in a phase 2 study. Int J Radiat Oncol Biol Phys 2015; 91(4): 730–736. doi: 10.1016/j.ijrobp.2014.11.027.

30. Prada PJ, Fernández J, Martinez AA et al. Transperineal injection of hyaluronic acid in anterior perirectal fat to decrease rectal toxicity from radiation delivered with intensity modulated brachytherapy or EBRT for prostate cancer patients. Int J Radiat Oncol Biol Phys 2007; 69(1): 95–102. doi: 10.1016/j.ijrobp.2007.02.034.

31. Chapet O, Udrescu C, Tanguy R et al. Dosimetric implications of an injection of hyaluronic acid for preserving the rectal wall in prostate stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2014; 88(2): 425–432. doi: 10.1016/j.ijrobp.2013.10.039.

32. Wilder RB, Barme GA, Gilbert RF et al. Cross-linked hyaluronan gel improves the quality of life of prostate cancer patients undergoing radiotherapy. Brachytherapy 2011; 10(1): 44–50. doi: 10.1016/j.brachy.2009.12.005.

33. Prada PJ, Gonzalez H, Menéndez C et al. Transperineal injection of hyaluronic acid in the anterior perirectal fat to decrease rectal toxicity from radiation delivered with low-dose-rate brachytherapy for prostate cancer patients. Brachytherapy 2009; 8(2): 210–217. doi: 10.1016/j.brachy.2008.11.010.

34. Prada PJ, Jimenez I, González-Suárez H et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction and transperineal hyaluronic acid injection into the perirectal fat for the treatment of favorable stage prostate cancer: treatment description and preliminary results. Brachytherapy 2012; 11(2): 105–110. doi: 10.1016/j.brachy.2011.05.003.

35. Peckinpaugh JL, Reddy HS, Tower RN. Large particle hyaluronic acid gel for the treatment of lower eyelid retraction associated with radiation-induced lipoatrophy. Ophthalmic Plast Reconstr Surg 2010; 26(5): 377–379. doi: 10.1097/IOP.0b013e3181cc85b0.

36. Wu WJ, Gao Y, Liu SM et al. Subcutaneous injection of hyaluronic acid to decrease acute skin toxicity after adjuvant interstitial brachytherapy in parotid gland cancer patients: a nonrandomized controlled trial. J Oral Maxillofac Surg 2020; 78(1): 167–172. doi: 10.1016/j.joms.2019.09.005.

37. Barber C, Powell R, Ellis A et al. Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: a preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis. Support Care Cancer 2007; 15(4): 427–440. doi: 10.1007/s00520-006-0171-1.

38. Murakami N, Shima S, Kashihara T et al. Hyaluronic gel injection into the vesicovaginal septum for high-dose-rate brachytherapy of uterine cervical cancer: an effective approach for bladder dose reduction. J Contemp Brachytherapy 2019; 11(1): 1–7. doi: 10.5114/jcb.2019.82612.

39. Liguori V, Guillemin C, Pesce GF et al. Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. Radiother Oncol 1997; 42(2): 155–161. doi: 10.1016/s0167-8140(96)01882-8.