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Analgesic Effect of 35 kDa Hyaluronan Fragment on Vaginal Oocyte Retrieval Operation-Associated Pain: A Case Report

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Abstract

Transvaginal oocyte retrieval (TVOR) is a common yet painful procedure in assisted reproductive technologies (ART) like in vitro fertilization (IVF). Effective pain management during and after TVOR is essential, particularly since anesthesia may influence oocyte quality and treatment outcomes. This case report aims to evaluate the analgesic efficacy of 35 kDa hyaluronan fragments (HA35) to manage TVOR-associated pain. A 40-year-old patient with infertility underwent two TVOR procedures ten months apart under nearly identical preparatory conditions, including a subcutaneous injection of recombinant human chorionic gonadotropin to stimulate oocyte maturation. During the first procedure, pain management consisted of diclofenac sodium suppositories alone, while the second procedure included additional subcutaneous and topical HA35 administration alongside diclofenac sodium. The primary outcome measured was the patient's self-reported pain level on the Numeric Pain Rating Scale (NPRS), alongside secondary indicators of postoperative recovery and discomfort. Results demonstrated that the addition of HA35 reduced the patient's pain score by half, shortened the duration of pain, significantly improved comfort, and prevented postoperative bleeding, allowing for immediate discharge. This case suggests that HA35 may offer an effective, low-risk approach to enhance analgesia, reduce side effects, and improve patient recovery in TVOR procedures.

Keywords

Transvaginal Oocyte Retrieval, 35 kDa Hyaluronan Fragments HA35, Analgesia, Pain Relief, Wound Healing

1. Introduction

Transvaginal oocyte retrieval (TVOR), also known as oocyte collection, is widely used procedure in assisted reproductive technologies (ART) such as in vitro fertilization (IVF), especially for patients with infertility [1]. Before TVOR, women typically receive an intramuscular or subcutaneous injection of human chorionic gonadotropin (hCG) to induce oocyte maturation. Approximately 30 to 40 hours after hCG administration, oocytes are retrieved by using an ultrasound-guided needle through the vaginal wall into the ovarian follicles [2]. TVOR, a significant advancement in ART, offers a less invasive option than transabdominal or laparoscopic methods [3]. Its simplicity and efficiency make it the gold standard in ART procedures [4]. However, TVOR is not without risks, including potential injury to surrounding tissues and complications [5] [6]. The most common complications include pain during and after the procedure, often accompanied by increased vaginal discharge and spotting. To manage these symptoms, physicians typically recommend anti-inflammatory medications and advise avoiding strenuous activities. Common pain management approaches include conscious sedation, general anesthesia, patient-controlled analgesia, regional anesthesia, and medications like propofol and diclofenac sodium. Of these, conscious sedation with rectal diclofenac sodium is widely used due to its minimal side effects and good tolerability [7]-[9]. However, variability in pain relief and potential gastrointestinal side effects can contribute to patient anxiety, potentially impacting outcomes.

Studies suggest that combining analgesics rather than using a single agent may be more effective in reducing pain while minimizing side effects [10]. Hyaluronan, a naturally occurring component in connective tissues, shows promise as an adjunct for reducing inflammation and pain across various conditions, including cancer pain, neuropathic pain, and orthopedic inflammatory pain [11]-[13]. The low molecular weight hyaluronan fragment (35 kDa, HA35) has shown potential to interact with transient receptor potential cation channel subfamily V member 1 (TRPV1), which may contribute to its analgesic effects.

In this report, we examine a novel approach to managing TVOR-associated pain by combining HA35 with diclofenac sodium in a 40-year-old patient undergoing two TVOR procedures. The first procedure utilized diclofenac sodium alone, while the second combined it with HA35. This report aims to assess HA35's analgesic efficacy and safety in reducing pain, minimizing side effects, and enhancing comfort and recovery in ART procedures, providing insights into improved pain management strategies for TVOR.

2. Case Report

2.1. Patient Overview and Medical Background

The patient is a 40-year-old Chinese woman who sought consultation at multiple reproductive medicine departments after years of unsuccessful attempts at natural conception. She is in good health, with a height of 168 cm, a weight of 55 kg, and

a body mass index (BMI) of 19.5 kg/m^2. She has no history of genetic disorders, surgeries, or drug allergies. Hormonal tests revealed abnormal levels of estradiol and progesterone. Combined with ultrasound findings, she was diagnosed with ovarian insufficiency, ovarian endometriotic cysts, and infertility. Given the advancements in ART, the reproductive medicine physician recommended TVOR followed by IVF to assist in conception. The patient consented to proceed with IVF as advised. Prior to the oocyte retrieval, the patient followed the physician's instructions to enhance ovarian function through traditional Chinese medicine, acupuncture, and moderate exercise. Once her estradiol and progesterone levels normalized, the TVOR procedure was scheduled (Table 1). To trigger oocyte maturation, the patient received a single subcutaneous injection of 250 μg of recombinant human chorionic gonadotropin in the abdominal subcutaneous fat 35 hours before the procedure. For anesthesia, the patient was administered a 100 mg rectal diclofenac sodium suppository one hour before the procedure and was prescribed oral Cefuroxime Axetil tablets (one tablet, twice daily for three days) starting two hours postoperatively to prevent infection. After anesthesia, the vagina was irrigated with a saline solution. Under ultrasound guidance, the TVOR needle was inserted through the vaginal wall into the ovarian follicles. The needle was connected to a suction device used to aspirate follicular fluid containing cellular material, including oocytes. Unfortunately, the first procedure failed due to poor oocyte quality, which prevented successful fertilization.

Table 1. Preoperative estrogen six-hormone panel results.

	First Procedure	Second Procedure	Reference Range
Estradiol (E2)	371.00 pmol/L	266.10 pmol/L	Follicular Phase: 114 - 332 pmol/L
Progesterone(P)	1.62 nmol/L	0.45 nmol/L	Follicular Phase: <0.159 - 0.616 nmol/L
Luteinizing Hormone (LH)	3.40 mIU/mL	3.01 mIU/mL	Follicular Phase: 2.4 - 12.6 mIU/mL
Follicle-Stimulating Hormone (FSH)	6.05 mIU/mL	5.34 mIU/mL	Follicular Phase: 3.5 - 12.5 mIU/mL
Testosterone (T)	0.854 nmol/L	1.350 nmol/L	0.29 - 1.67 nmol/L

2.2. Treatment Protocol and Outcomes

The patient continued with the prescribed treatment regimen and underwent a second TVOR procedure ten months later. To address the oocyte quality issues encountered during the first retrieval, which could affect fertilization success, she received two additional autologous T lymphocyte stem cell injections during the treatment period at our laboratory. Additionally, in response to feedback about the inadequate analgesic effects during the first procedure, we recommended incorporating HA35 to further reduce inflammation, pain, and side effects associated with TVOR. HA35 was prepared by mixing hyaluronidase injection (H31022111,

SPH No. 1 Biochemical & Pharmaceutical Co., Ltd.) with hyaluronan injection (H20174089, Shanghai Haohai Biotechnology Co., Ltd.). With the patient's consent, she received a subcutaneous injection of 100 mg/5mL HA35 in the abdominal fat three hours before the procedure and again 24 hours postoperatively. Additionally, a HA35-containing gel was applied to the vaginal area and surrounding tissues after the procedure. All other aspects of the procedure remained consistent with those of the first TVOR. The second oocyte retrieval was highly successful, yielding five oocytes. Intracytoplasmic sperm injection (ICSI) was performed on all five oocytes, resulting in three morphologically abnormal oocytes and two high-quality embryos. Ultimately, one blastocyst successfully developed (**Figure 1**).

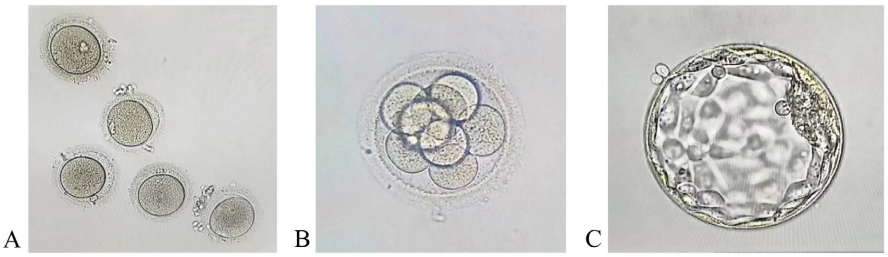

Figure 1. Oocyte retrieval and embryo development. A: 5 oocytes retrieved: 2 MII mature oocytes, 2 MI immature oocytes, 1 GV oocyte. B: Cleavage stage with 2 high-quality embryos. C: Blastocyst stage with 1 blastocyst, morphology rated 4 BB.

2.3. Pain Management and Comparisons

We analyzed the pain and symptoms experienced by the patient during both oocyte retrieval procedures, using the Numeric Pain Rating Scale (NPRS) to assess and compare postoperative pain levels. As shown in **Table 2**, the patient reported a postoperative pain score of 6 out of 10 following the first procedure, which decreased to 4 after 2 hours. Resting in bed for 3 hours before discharge, her pain level reduced to 3, and she chose to take a taxi home. The pain subsided completely after 6 hours, although she experienced some vaginal discharge and discomfort. Sleep was unaffected, but some discomfort persisted the following day. Ten months later, after the second oocyte retrieval, the patient reported a significantly lower pain score of 3. This time, she did not need to rest in bed and was able to leave the hospital immediately, opting for the subway home. Pain had nearly disappeared within 2 hours, with no vaginal discharge or discomfort reported.

At follow-up appointments one week and one month after each procedure, the patient was asked about her postoperative experience, healing progress, and overall impressions of the analgesic approaches. After the first procedure, she expressed concerns regarding prolonged discomfort and gastrointestinal effects from diclofenac sodium. In contrast, following the second procedure, the patient noted that pain management with the HA35 combination was not only more effective but also provided a smoother and faster recovery with no side effects.

Table 2. Evaluation of drug administration and postoperative pain-related symptoms in patients undergoing two TVOR surgeries.

		First Procedure	Second Procedure
Anesthesia		1 hour before surgery: Rectal administration of 50 mg diclofenac sodium suppository, administered twice for a total of 100 mg.	1. 1 hour before surgery: Rectal administration of 50 mg diclofenac sodium suppository, administered twice for a total of 100 mg. 2. 3 hours before and 24 hours after surgery: Subcutaneous injection of HA35 into abdominal fat.
Infection Prevention		Prescribed oral Cefuroxime Axetil tablets (one tablet, twice daily for three days) two hours after surgery.	1. Post-surgery: Application of HA35 gel inside and around the vaginal area. 2. Prescribed oral Cefuroxime Axetil tablets (one tablet, twice daily for three days) two hours.
Postoperative Pain	0 h	6	3
	2 h	4	1
	3 h	3	0
	6 h	0	0
Other Symptoms		1. Bed rest for 3 hours before discharge. 2. Mild vaginal discharge and discomfort. 3. Sleep was good, but discomfort persisted the next day.	1. Immediate discharge without bed rest. 2. No vaginal discharge or discomfort. 3. Good sleep with no residual discomfort.

3. Discussion

Infertility remains a global concern, affecting approximately one in six people worldwide, according to the latest report from the World Health Organization. Since the introduction of IVF 46 years ago, millions of children have been born through IVF and other ART. TVOR is a crucial component of IVF, often considered one of the more stressful and painful aspects of the process. Complications such as bleeding, infection, and severe pain are common following the procedure [14]. A clinical study by Gungor on TVOR-related complications identified pain as the most frequent issue, with 45 out of 789 patients (5.7%) experiencing severe pain, a rate higher than previously reported [15]. In contrast, Ludwig *et al.* reported that 3.1% of patients experienced severe to extreme pain following oocyte retrieval [16]. Other studies have also indicated that the longer the duration of the TVOR procedure, the more prolonged the pain [17]. Consequently, preoperative anesthesia is a critical step in alleviating patients' fears of the procedure. However, the choice of anesthetic is complicated by the potential presence of anesthetic agents in the follicular fluid, which may impact oocyte quality and, subsequently, IVF fertilization and implantation rates [18].

Fortunately, the type of anesthesia used during oocyte retrieval is often tailored to the patient's expected oocyte yield, pain anxiety, and the facilities available at

the ART center [19]. For instance, local anesthesia may be chosen if fewer than five oocytes are expected. In this case, the patient was clinically diagnosed with low oocyte quality and quantity, so rectal administration of diclofenac sodium suppositories was used as the local anesthetic for both retrieval procedures. Diclofenac sodium, an NSAID, works by inhibiting cyclooxygenase (COX) enzymes, which reduces prostaglandin synthesis. This decreases peripheral nerve sensitivity to pain and provides both analgesic and anti-inflammatory effects. It is generally considered safe and has well-documented analgesic efficacy when administered rectally [20], although gastrointestinal and neurological side effects are not uncommon. In this case, the patient experienced transient gastrointestinal discomfort after using diclofenac sodium suppositories alone and reported significant pain during the first TVOR procedure. Based on these findings, we introduced HA35 in combination with diclofenac sodium for the second procedure. HA35 is a low molecular weight fragment of hyaluronan produced by enzymatic digestion of high molecular weight hyaluronan using recombinant human hyaluronidase PH20 or hyaluronidase PH20 extracted from bovine or human testes [21]. Clinically, HA35 has been studied for its analgesic properties in inflammatory pain affecting areas such as the shoulders, neck, back, and temporal regions, as well as for neuropathic pain associated with herpes zoster, cancer pain, and bone metastasis pain. It has demonstrated significant efficacy with minimal side effects and has been shown to reduce the side effects of corticosteroids [22]-[24]. The effective analgesic mechanism of HA35 may be related to its interaction with the transient receptor potential cation channel subfamily V member 1 (TRPV1) channel, a capsaicin-sensitive pain receptor.

In this case report, the patient assessed the analgesic effects of diclofenac sodium suppositories during both procedures (**Table 2**). The combined use of diclofenac sodium and HA35 during the second procedure resulted in a postoperative pain score that was reduced by half compared to the use of diclofenac sodium alone. Additionally, the patient reported improved physical well-being and less discomfort after the second procedure. These results suggest that the combination of HA35 with diclofenac sodium more effectively reduced TVOR-related pain and discomfort and accelerated wound healing, as evidenced by the absence of bloody vaginal discharge. Therefore, the study indicates that HA35 (**Tables 1-2**) not only alleviates TVOR-associated pain but also enhances healing and comfort, demonstrating a superior safety profile compared to conventional medications.

Furthermore, it is noteworthy that the success of the patient's TVOR is closely linked to the stem cell injection treatment, with the two stem cell therapies significantly improving oocyte quality. A case report from the University of Illinois also indicates that mesenchymal stem cells can increase estrogen production and alleviate menopausal symptoms in women with premature ovarian failure [25]. Therefore, stem cell therapy may represent a promising avenue for reproductive medicine that merits further exploration and integration. This case report also provides valuable insights into the potential applications of stem cells in women's

reproductive health.

4. Conclusion

The combination of subcutaneous injection of low molecular weight hyaluronan (HA35) into the abdominal fat tissue and rectal administration of diclofenac sodium suppositories effectively alleviated the pain and discomfort associated with the TVOR procedure. This innovative approach not only reduced postoperative pain scores by half compared to using diclofenac sodium alone but also shortened the duration of pain while improving the patient's overall well-being and comfort. The addition of HA35, known for its analgesic and anti-inflammatory properties, demonstrated a superior safety profile, minimizing the side effects often associated with traditional analgesics. Furthermore, the absence of complications such as bloody vaginal discharge indicated accelerated wound healing. These findings suggest that HA35, when used alongside established analgesics, can enhance pain management strategies in reproductive medicine, potentially leading to improved patient experiences during IVF procedures.

Consent for Publication

Written informed consent was obtained from the patient, and the patient consented to the publication of all images, clinical data, and other information included in the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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