Original Article

The Effect of a Newly Designed Needle on the Pain and Bleeding of Patients During Oocyte Retrieval of a Single Follicle

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Abstract

Background: The purpose of this study was to evaluate the effect of needle type on pain and bleeding during oocyte pick-up (OPU).

Methods: From May through November 2013, patients undergoing OPU from a single follicle without any analgesic treatment were including this study. Eligible patients (n=75) were randomized 1:1 to undergo the procedure with either a reduced needle (17 gauge body, 20 gauge tip; RN group) or a standard needle (19 gauge; SN group). Overall pain was assessed by patients using a visual analogue scale (VAS), and vaginal bleeding after the procedure was recorded. Fisher exact, t-test or Wilcoxon test were used, and $p<0.05$ was considered to be statistically significant.

Results: The percentage of mature oocytes was 86.5% in the RN group and 91.7% in the SN group. Pain during OPU was significantly lower in the RN group than in the SN group (mean VAS score±SD: 3.2±2.0 *cm vs*. 4.9±2.2 *cm*, $p<0.01$; mean±SD). The frequency of vaginal bleeding was also significantly lower in the SN group (26.3% *vs*. 48.6%; $p<0.05$). The frequency of bleeding in the RN group was also significantly lower than that in the SN group (26.3% *vs*. 48.6%; $p<0.05$). No significant differences were found between the two groups with regard to fertilization and pregnancy rates.

Conclusion: The newly designed needle significantly reduced pain and vaginal bleeding associated with single-follicle OPU in patients receiving no analgesic treatment, in comparison with a standard needle. The RN had no adverse effect on the quality of retrieved oocytes.

Keywords: Aspiration needle, Bleeding, Oocyte aspiration, Pain.
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Introduction

Transvaginal ultrasound-guided oocyte pick-up (OPU) for assisted reproductive technology (ART) treatment was first reported in 1985 (1). Since then, this technique has been rapidly widespread throughout the world, as a replacement for laparoscopic oocyte retrieval. It is now an indispensable technique in ART treatment.

Currently, the ovarian stimulation protocol for ART treatment is changing from hyperstimulation to mild or minimal stimulation protocol by minimizing the dose of parenteral follicle stimulation or shifting to oral medicine (2). As a result, the number of follicles punctured and oocytes retrieved during OPU has decreased. In our clinic, the average number of retrieved oocytes among patients aged 37-40 years has been reported as 3.7 (3), and no anesthesia (either local or general) is used during OPU in more than half of our patients. However, even when only a single follicle is punctured, oocyte retrieval can be painful. Therefore a method for reducing pain during oocyte retrieval is needed, particularly for cases where anesthesia is not used.

Recently, a newly designed needle for OPU was launched with the aim of reducing pain during OPU (4). The tip of the needle (*i.e.* the last 50 *mm*, the part that penetrates into the tissues) is thinner than standard, with the remainder of the needle having a larger diameter. An initial study showed that overall pain experienced during OPU with the reduced needle was significantly lower than that with the standard needle (4). However, there were limitations with that study: several follicles were aspirated during each procedure, and local anesthesia was administrated. For studies investigating the effect of a new needle, it is important to ensure that number of aspirated follicles is the same in both study groups and that perceived pain is not masked by analgesic treatment. Therefore, in the present study, an attempt was made to evaluate the effect of reduced needle on pain and vaginal bleeding associated with single-follicle OPU in patients who did not receive any analgesic treatment.

Methods

Patients: From May through November 2013, 100 patients were screened for the study and 75 were enrolled (Figure 1). Twenty-five screened patients could not be enrolled in this study because they ovulated before planned oocyte aspiration. All randomized patients were treated with the needle they had been assigned to. Therefore, there were no protocol violations and all analyses were performed according to the intention to treat. No patient was lost to follow-up. In all patients, ovarian follicles were matured by either a natural cycle or a clomiphene citrate cycle. Signed informed consent was obtained from all patients, and this study was approved by the Institutional Board of the Sugiyama Clinic.

The study was registered with the UMIN Clinical Trials Registry, study number UMIN000014 800. Patients were randomized on the day of oocyte retrieval into either the reduced needle (RN) group or the standard needle (SN) group, with a 1:1 allocation ratio. The needle used for the procedure was not known to the patient but for practical reasons it was known to the treating physician.

Oocyte aspiration: All OPU procedures were performed transvaginally, by a single physician, with ultrasonography to guide the needle. No anesthesia or analgesic agents were used. Patients were randomly assigned to one of the two groups on the day of oocyte aspiration. In each case, a single follicle with a mean diameter of >17 *mm* was aspirated, using either a reduced needle with a 17 gauge body and a 20 gauge tip (Sense®, Vitrolife, Sweden; RN group) or a standard 19 gauge needle (UNIEVER oocyte aspiration needle®, Japan; SN group). All needles were connected to a syringe (via a Luer connection) for manual suction, meaning that the aspiration pressure could be controlled as needed. If an oocyte could not be retrieved following puncture, follicle flushing was performed up to 5 times.

Rating of pain and evaluation of bleeding

Primary endpoint: Pain was rated by each patient immediately after the OPU by means of a visual analogue scale (VAS), comprising a vertical line from 0 *cm* (no pain) to 10 *cm* (unbearable pain) (5). All patients were asked by the same medical doctor to mark the VAS with their rating of the overall pain for the whole procedure.

Secondary endpoint: The pain perceived by patients 30 *min* after the procedure, captured in the same way as overall pain, was a secondary endpoint.

Bleeding from the vaginal wall (at the point of needle penetration) was also evaluated after OPU. "Bleeding" was defined as continuous signs of bleeding even after the application of direct compression for 30 *s*, and "no bleeding" defined as cessation of blood loss after direct compression.

The numbers of fertilized oocytes and pregnancies were compared between the two groups.

IVF procedure and embryo transfer: The *in vitro* fertilization (IVF) procedure used in the present study has been described previously (6). The retrieved oocyte was fertilized by conventional insemination or intracytoplasmic sperm injection (ICSI) three to five hours after follicle aspiration. Oocytes were examined using a dissecting microscope, 16-18 *hr* after insemination or ICSI. The presence of two pronuclei with extrusion of the second polar body was taken as the evidence of successful fertilization.

Patients acquiring embryos underwent embryo transfer on day 2 or day 3. Embryos were evaluated microscopically before transfer, and those with more than seven blastomeres and less than 10% fragmentation were classified as morphologically good-quality embryos (MGEs) (7). Embryos were placed transcervically into the uterus using a soft ET catheter (Kitazato, Japan) (8).

Pregnancy was recognized when the development of a gestational sac was evident from trans-

vaginal ultrasound on the 21st day after embryo transfer.

Sample size calculation and statistical analysis: Single-follicle oocyte retrieval without anesthesia is routinely performed at our clinic. The level of pain associated with the procedures is higher when it is performed without anesthesia, and the average VAS score for the primary endpoint "overall pain experience" was anticipated to be 5.0 *cm* with the standard needle. Based on a study by Wikland et al. (4), a standard deviation of 2.0 *cm* was anticipated. The reduced needle was expected to reduce the VAS pain score by 1.2 *cm* (24%), a clinically significant difference. Forty-four patients would be needed in each study group to demonstrate this difference with 80% power and a significance level of 0.05 (two-tailed tests).

Fisher's exact test was used to analyze dichotomous data and student's t-test and Wilcoxon test when normality distribution was rejected were used for continuous variables. A p-value of <0.05 was considered statistically significant.

Results

Seventy five patients were enrolled into the study and were randomized. Next, they underwent OPU with either the RN or the SN (Figure 1). The number of patients enrolled was lower than estimated in the sample size calculation. Patients' baseline characteristics and data relating to the OPU procedure are summarized in table 1. The average age in the RN group was 40.8±3.9 years, compared with 40.3±3.6 years in the SN group. The mean number of retrieved oocytes was 0.97±0.16 in the RN group and 0.97±0.16 in the SN group, while the percentages of mature oocytes were 86.5% and 91.8% in the two groups, respectively. Overall, there were no significant differences between the two groups in baseline characteristics or OPU procedure data.

There was no significant difference in fertilization rate between the RN group and SN group (Table 2). The pregnancy rate was numerically higher in the RN group (33.3% *vs*. 16.6%), although this difference did not reach statistical significance (Table 2).

The results relating to pain are shown in table 3. The mean VAS score for overall pain experienced during OPU was 3.2±2.0 *cm* in the RN group, significantly lower than the one in the SN group 4.9±2.2 (p<0.01). There was no significant difference in pain experienced 30 *min* after OPU be-

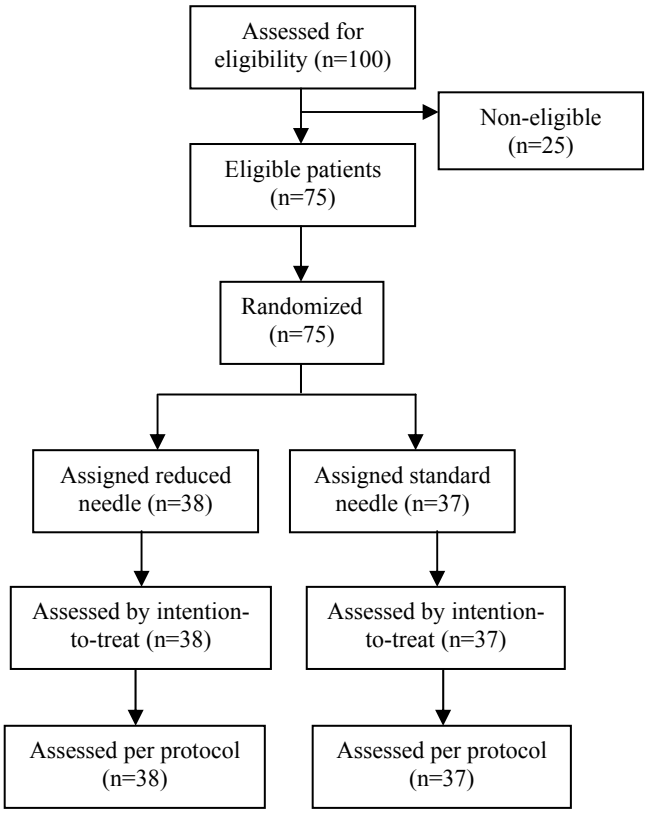

Figure 1. Flow chart showing patients' progression through the study

Table 1. Baseline characteristics and oocyte pick-up (OPU) procedure data in the reduced needle (RN) and standard needle (SN) groups

	RN group	SN group	P-value
Patients (n)	38	37	
Age (years) *	40.8±3.9	40.3±3.6	NS
Previous OPU attempts * **(n)**	6.0±5.8	5.2±2.6	NS
Previous pregnancy * **(n)**	0.9±1.3	1.1±1.3	NS
Previous delivery * **(n)**	0.1±0.4	0.2±0.5	NS
Punctured follicles * **(n)**	1.0	1.0	NS
Retrieved oocytes * **(n)**	0.97±0.16	0.97±0.16	NS
Percentage of matured oocytes, % (n)	86.5(32/37)	91.7 (33/36)	NS
OPU time, seconds *	40.9±3.9	40.1±3.6	NS

*Mean±SD; NS: Not Significant

Table 2. Assisted reproductive technology (ART) outcomes in the reduced needle (RN) and standard needle (SN) groups

	RN group	SN group	p-value
Fertilization rate, % (n)	87.5% (28/32)	81.8% (27/33)	NS
Embryo transfer cycles (n)	15	18	
Transferred embryos (n)	15	18	
Percentage of MGEs, % (n)	66.7% (10/15)	66.7% (12/18)	NS
Pregnancy rate, % (n)	33.3 (5/15)	16.6 (3/18)	NS

MGEs: Morphologically Good-Quality Embryos; NS: Not Significant

Table 3. Pain and frequency of bleeding in the reduced needle (RN) and standard needle (SN) groups

	RN group	SN group	p-value
Overall pain experience during OPU (VAS, *cm*) *	3.2±2.0	4.9±2.2	0.008
Pain experience 30 *min* after OPU (VAS, *cm*) *	0.8±1.2	0.6±1.2	NS
Frequency of bleeding, % (n)	26.3% (10/38)	48.6% (18/37)	0.042

* Mean±SD; NS: Not Significant

tween-groups. The frequency of bleeding from the vaginal wall after OPU was reduced by 26.3% in the RN group compared with the SN group ($p<0.05$; Table 3).

Discussion

Anesthesia is an established method for reducing pain during OPU (9). Another strategy is to use a thinner needle for the procedure. In the present study, overall pain during oocyte aspiration was significantly lower with a newly designed "reduced" needle with a thinner tip, in comparison with the standard needle. Furthermore, vaginal bleeding was lower with the RN than with the SN. No negative effects were found with the RN group in relation to oocyte fertilization, embryo morphology, or pregnancy rate.

It is difficult to evaluate pain experience during OPU, because many factors can have an influence such as fear of pain, anxiety, physician's skill, operation time and technical factors including needle diameter and sharpness during OPU. Analgesia is another potential factor, although that was not the case here because analgesic was not used. In a previous study of the RN, all patients received local anesthetic using paracetamol and had paracercivcal block with lidocaine (4). Moreover, all patients received ovarian stimulation, meaning that several follicles were aspirated and the total OPU time was longer than the time in the present study. Under such conditions, it may be difficult to evaluate accurately the effect of the RN on pain. In the present study, it was hoped that the effect of the RN might be more obvious because patients had only one follicle aspirated and no analgesic drugs were used. In addition, to avoid possible bias related to multiple operators, all OPUs were performed by a single physician in the present study. Consequently, a reduction in VAS pain score was observed from 4.9 to 3.2 *cm*, a much larger relative reduction than in the previous study where corresponding VAS scores were 2.6 and 2.1 *cm*.

Too much reduction of the needle diameter risks damaging the oocytes, although few studies have investigated this issue. With bovine oocytes, it has been demonstrated that both the diameter and bevel of the needle, as well as the aspiration vacuum, affect the recovery rate and developmental competence of oocyte (10, 11). Previous investigation of the RN used in the present study concluded that human oocytes are unaffected by using a needle with a 20 gauge tip and an aspiration pressure of 90-120 *mmHg* (4). The present data are in agreement with those findings.

Previously, a prototype needle similar to the RN investigated in this study was created. Like the needle reported here, the prototype had a Luer connection, a 17 gauge body and a 20 gauge tip. It was hand-made by connecting two needles with different diameters. The oocyte recovery rate with this needle was comparable with that of a conventional needle. However, approximately 50% of retrieved oocytes had degenerated and it was concluded that the prototype needle was harmful for oocytes (data not shown). This may be attributable to the way in which the prototype was made: where the two constituent needles was joined, the inner wall would not have been smooth and the flow of fluid passed this point would potentially have been turbulent. The RN used in the present study appears to have overcome this problem.

Since the study was performed by a single physician on single-follicle oocyte retrievals with no analgesic treatment, patient perceived pain and physician perceived bleeding could be appropriately studied. Still, one potential limitation of the current study was the relatively small number of the patients recruited. However, statistical analysis demonstrated that the study had sufficient power to detect an important difference. It was also thought that the patients would like to change our clinical practice quickly, taking into account the outcome of the study. Another potential limitation of the study was that the type of needle was not blind to the physician. However, since the technique and average OPU time were the same in both groups, it is unlikely that this would impact the results.

This needle is not only useful for single-follicle oocyte retrievals in patients with no analgesic treatment but also more broadly in patients with fear of aspiration and those with a low threshold for pain. It will also be useful for patients with a history of bleeding and patients undergoing fertili-

ty preservation in conjunction with blood cancer treatment such as leukemia or lymphoma.

Conclusion

Patient perceived pain during single-follicle oocyte retrieval without analgesic was significantly lower with the newly designed–aspiration needle with a thin tip than with a standard needle. In addition, post-procedural bleeding from the vaginal wall was lower with the RN. The RN had no adverse effect on the quality of retrieved oocytes.

Conflict of Interest

The newly designed needles for this study were provided free of charge by the manufacture, Vitrolife. However, the authors have received no funding for this study, and they have no financial interest in Vitrolife or any of the other companies whose products were used. Therefore, there are no competing interests.

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