

—Mini Review—

Evidence-based Anesthesiology for ART

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Abstract: Anesthesia for ART procedures have been provided by a variety of anesthetic methods including sedation, regional anesthesia, and general anesthesia. Anesthetic management should be safe, and provide rapid recovery for those women undergoing procedures that are often performed on an ambulatory basis. During ART procedures, anesthetic agents are gradually transferred into follicular fluid. Laboratory studies have suggested that local anesthetic agents, nitrous oxide, volatile halogenated agents, and some intravenous agents, such as propofol, interfere with some aspects of reproductive physiology *in vitro*. However, there is little clinical data suggesting that brief administration of any of the currently used anesthetic agents for ART procedures adversely affect live birth rates. The concern for antiemetics and NSAIDs use around ART procedures warrants further study. Identification of agents and techniques that provide optimal analgesia or anesthesia with negligible impact on ART success remains an important task for anesthesiologists.

Key words: Assisted Reproductive Technology, Anesthetic agent, Propofol, Reproductive outcome

Procedures for assisted reproductive technology, such as transvaginal oocyte retrieval and GIFT, often have accompanying pain in women, who are already suffering from the physical and psychological stress of infertility. Anesthesia for such procedures would reduce their suffering and may also enhance the ease of the procedures.

However, anesthetic agents, such as propofol, are detected in the follicular fluid during brief administration to the patient. Thus, the anesthetic method for ART procedures must entail minimal impact on the reproductive outcome of ART procedures, while assuring safety of the patients. As these procedures are usually performed on an ambulatory basis, short-acting anesthetic agents with minimal side effects are

desired.

A variety of anesthetic agents and methods have been used for ART, and there is no consensus as to the best method of anesthetic management for oocyte retrieval. For example, our primary anesthetic methods for transvaginal oocyte retrieval for *in vitro* fertilization (IVF) changed from epidural anesthesia to sedation with diazepam/ketamine, and subsequently to the current method of propofol based general anesthesia. The effects of anesthetic agents/methods on reproductive outcome are still vigorously being investigated. On the other hand, GIFT procedures are usually done under general anesthesia, and there is evidence that the currently used anesthetic agents, including nitrous oxide, are acceptable for this procedure.

This article will review the current status of anesthesia care in Japan and other countries, and then summarize the effects of anesthetic agents on the quality of anesthesia and reproductive outcome in IVF and GIFT.

Survey of anesthesia care for oocyte retrieval

As a standard anesthetic technique for transvaginal oocyte retrieval has not been established, a survey of the current anesthesia practice in different institutions or countries is of interest. Terui *et al.* conducted a nationwide survey in Japan in 2000 [1]. Among the 474 registered institutions, 312 (65.8%) responded. The most frequently employed anesthesia method was intravenous sedation and analgesia (61%), followed by general anesthesia (41%), and regional anesthesia (19%) (Fig. 1). The most frequently used anesthetic agent was the diazepam/pentazocine combination (54%), followed by ketamine/diazepam (14%). General anesthesia was provided by intravenous agents, such as thiopental (48%) and ketamine (32%), while propofol was only used in 17% of the institutions. Anesthesia was provided by the same obstetrician who performed oocyte retrieval in 73% of the institutions. Anesthesiologists were only involved in 11% of the

Received: March 29, 2005

Accepted: April 5, 2005

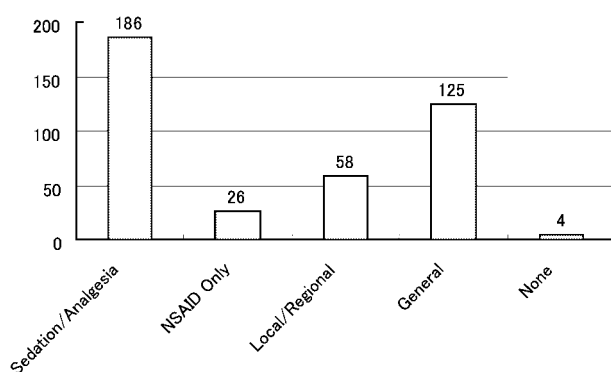


Fig. 1. Anesthesia method for oocyte retrieval in Japan (multiple answers were allowed).

institutions. Thus, the survey revealed a variety of anesthetic methods for oocyte retrieval in Japan, and that anesthesiologists were very infrequently involved.

Similar nationwide studies have been reported in the UK and USA. In the UK, Bokhari *et al.* [2] surveyed 58 centers performing IVF in 1997 and showed a similar trend in the choice of anesthesia method, i.e., sedation (48%), general anesthesia (29%), and regional anesthesia (13%). Both inhalational agents and intravenous agents were used, propofol being the most popular induction agent (90%). Of interest was that NSAIDs were used as a systemic analgesic in 25% of the institutions, which is quite contrary to the reluctance to use NSAID in the US (Scott Segal M.D., personal communication).

Contrary to the UK and Japan, the US practice is more uniform, with conscious sedation being performed in 95% of the institutions in 1997. Only 5% used either general, regional, or local anesthesia. Midazolam, propofol, and fentanyl were the most frequently used anesthetic/analgesic agents [3]. From these surveys, it is evident that the best anesthetic method or agent for oocyte retrieval is still under debate.

Effect of anesthetic agents on reproduction

Starting with the initial report by Boyers in 1987 in which oocytes from patients who received general anesthesia were less likely to be fertilized if the case duration was prolonged [4], the effects of anesthetic agents or methods on oocyte fertilization, early embryo development, and implantation have been actively investigated.

Pharmacokinetic studies have shown that most anesthetic agents are detected in the follicular fluid

during oocyte retrieval or GIFT. For example, propofol was detected 15 minutes after the start of administration, and the follicular propofol concentration gradually increased to about one tenth of the serum concentration as the procedure continued [5]. Both thiopental and thiamylal can be detected in follicular fluid within 11 minutes of administration for induction of general anesthesia in patients undergoing GIFT procedures. Fentanyl and alfentanil were detected in extremely low follicular concentrations when given for oocyte retrieval. The follicular fluid concentration of alfentanil was one tenth of that of the serum. On the other hand, midazolam was not found in follicular fluid of humans undergoing ART procedures, when used for anxiolysis and sedation.

A number of studies have noted that anesthetic agents may interfere with some aspects of the reproductive process in some species. A summary of such animal and human studies is shown in the attached table. This table was derived from a recent literature search of PubMed, as well as from the sources listed in the references. Each drug was assigned to one of three categories, i.e., 1) there is at least one study that showed no adverse effects on reproduction (○); 2) there are no relevant studies on this topic (△); and 3) there is at least one study that showed adverse effects (×). Caution is advised when interpreting this table because some of the studies in the first category may be underpowered and because some of the studies in the last category showed contradictory results. Also, in human studies, the effect of a drug on reproduction may have been masked or counterbalanced by the effect of an concomitantly administered anesthetic agent(s).

Among the commonly used anesthetic agents, propofol and nitrous oxide have been a source of controversy. Both of them are short-acting and suitable for ART procedures. Propofol has been associated with decreased development to the blastocyst stage and an increase in parthenogenetic activation [6]. Another study showed a decreased oocyte-sperm fusion test rate of fusion [7]. However, human studies have not shown decreased embryo scores nor decreased pregnancy rates between oocytes with higher follicular fluid propofol concentrations compared with oocytes with lower propofol concentrations, which were harvested earlier during oocyte retrieval. Thus far, most of the clinical studies of propofol on the reproductive outcome have failed to show any adverse effects when used for oocyte retrieval. There is only one study that may suggest adverse effects of propofol when used for

Table 1. Summary of the studies regarding the effects of anesthetic agents on reproduction

Drug	Animal study	Human study
Intravenous		
Propofol	× Decrease in sperm-ooxite fusion and blastocyst maturation. Parthenogenetic activation	○ 9 reports with no effect, 1 report with a decreased pregnancy rate (ZIFT, vs.thiopental-isoflurane)
Thiopental	△	○
Ketamine	○	○
Methohexital	△	△
Pentobarbital	× Oocyte maturation delay and chromosomally abnormal blastocyst	△
Diazepam	× Decrease in fertilization rate, egg degeneration, chromatin degeneracy, and meiotic arrest (contradictory)	△ No difference with propofol
Midazolam	○	○
Etomidate	△	× Decreased steroidogenesis including estradiol and progesterone
Opioid		
Fentanyl	○	○
Morphine	× Multiple sperm entered oocyte.	△
Meperidine	○	○
Alfentanil	○	○
Sufentanil	△	△
Remifentanil	○	○
Pentazocine	△	△
Buprenorphine	△	△
Butorphanol	△	△
Nalbuphine	△	△
Inhalational		
Sevoflurane	× Compound A causes sister chromatid exchange.	△
Isoflurane	× Decreased development to blastocyst	× Lower pregnancy rate with N2O/propofol than with remifentanil sedation
Halothane	× Mitosis arrest	× Lower pregnancy rate vs. enflurane for GIFT
Enflurane	△	○ Higher pregnancy rate than halothane
Desflurane	△	△
Nitrous oxide	× Reduced DNA synthesis and impaired mytotic spindle. Decrease in blastocyst development (depending on the stage of embryo development)	○
Local anesthetic		
Lidocaine	× Adverse effect on fertilization and embryo development, and embryo degeneration	○ Paracervical and epidural blocks
Mepivacaine	△	○ Epidural block
Bupivacaine	× Adverse effect only at high concentrations	△
Chlorprocaine	× Adverse effect on both fertilization and embryo development	△
Procaine	× Impaired zona reactions and polyploidy	△
Tetracaine	× Impaired zona reactions and polyploidy	△

○: There is at least one study that showed no adverse effects on reproduction, △: There are no relevant studies on this topic, ×: There is at least one study that showed adverse effects.

the ZIFT procedure when compared with thiopental-isoflurane [8]. Further investigation is necessary to elucidate the full effect of propofol on reproductive outcomes.

Adjuvant drugs that are used in the perioperative period also need to be evaluated with regard to reproductive outcome. These include NSAIDs for intra or postoperative analgesia and antiemetics to treat the side effects of anesthetic agents. The argument against the use of NSAID during ART procedures stems from the importance of prostaglandins during reproduction. However, we did not find any adverse reproductive

outcomes when diclofenac was used for analgesia after oocyte retrieval [9].

Antiemetics, such as metoclopramide and droperidol, may increase the prolactin level, which may adversely affect reproductive outcome. One study noted that metoclopramide rapidly induced hyperprolactinemia with subsequent impairment of ovarian follicle maturation and corpus luteum function in women [10]. Droperidol was found to significantly increase the prolactin level when used as part of a neuroleptanesthesia for GIFT, when compared with halothane anesthesia [11]. Fortunately, propofol is

normally infrequently associated with nausea, negating the need for these antiemetic agents.

Anesthesia for GIFT

The GIFT procedure is performed using laparoscopy, thus deserves special anesthetic considerations. Pneumoperitoneum causes significant hemodynamic and respiratory changes that are aggravated by the Trendelenburg position. The risk of endobronchial intubation is increased by these two maneuvers.

Laparoscopy usually requires general anesthesia. After induction with thiopental or propofol, fentanyl, and a muscle relaxant, anesthesia is maintained using one of the volatile anesthetic agents with or without nitrous oxide. As shown in the attached table, each volatile anesthetic agent may affect reproductive outcome in a different way. Caution is advised when selecting a volatile halogenated agent, especially when selecting a relatively new agent, because even its metabolites or by-products may adversely affect reproductive outcome.

Another method of general anesthesia for GIFT is propofol/nitrous oxide anesthesia. This technique has been found to cause less postoperative sedation, lower pain scores, and less emesis when compared to the isoflurane/nitrous oxide technique [8]. In a multi-center study, use of nitrous oxide during GIFT and ZIFT was not associated with a lower pregnancy rate [12].

Conclusion

Anesthesia for ART procedures should be safe and effective for patients, with negligible impact on ART success. Studies have suggested that many anesthetic agents, including propofol, interfere with some aspects of reproductive physiology *in vitro*. However, there is little clinical data suggesting that brief administration of any of the currently used anesthetic agents for ART procedures adversely affect live birth rates. Identification of agents and techniques that provide optimal analgesia or anesthesia with negligible impact on ART success remains an important task for anesthesiologists.

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