

Effects of General and Locoregional Anesthesia on Reproductive Outcome for In Vitro Fertilization: A Meta-analysis

The objective of this meta-analysis was to evaluate prospective trials of general or locoregional anesthesia on reproductive outcomes (cleavage and pregnancy rate) for in vitro fertilization (IVF). Of 115 published studies retrieved from a search of articles indexed on MEDLINE from 1966 to February 1999, four studies with distinct general and locoregional anesthesia were deemed eligible for meta-analysis. The pooled relative risk and odds ratios were calculated. A test for homogeneity was also performed. The pooled log odds ratio was 1.03 (95% CI 0.90-1.18) in cleavage rate and 0.71 (95% CI 0.47-1.08) in pregnancy rate. Heterogeneity was negative. Cleavage and pregnancy rates were not significantly different in both the general anesthesia and locoregional anesthesia groups. Both anesthetic techniques were favorable to IVF procedure by available published evidence when anesthesia was needed.

Key Words: Fertilization in Vitro; Anesthesia; Meta-Analysis

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INTRODUCTION

Patients undergoing in vitro fertilization may be exposed to various techniques of anesthesia used in assisting reproductive technology. Reports on the effectiveness of a single anesthetic agent or in combination with other drugs, including stress response to anesthesia, are currently inconclusive or are the subject of debate. Results of general anesthesia using inhalation agents, nitrous oxide, intravenous agents (especially propofol), and opioid analgesics are controversial (1-7). Instead of general anesthesia, local or regional anesthesia (epidural and paracervical block) are useful alternative anesthetic methods for assisted conception. Several clinical studies exploring the effects of anesthetic techniques using different drugs that affect reproductive outcomes have failed to consistently show differences in effect.

In this situation, a meta-analysis in which reviews systematically the literature may offer a solution. The quantitative information from several studies in which diverse, independent findings are integrated, can provide a statistical summary together with an appraisal of the uncertainties. The purpose of the current meta-analysis is to investigate whether general or locoregional anesthesia affects reproductive outcome when these techniques are applied to patients undergoing in vitro fertilization (IVF).

MATERIALS AND METHODS

The meta-analysis was performed according to prospectively defined clinical studies. Online retrieval MEDLINE records (from 1966 to February 1999) for English-language reports were searched using the following MeSH terms as the key and text words: "anesthesia and fertilization/or assisted reproductive technique, in vitro fertilization." The reference lists of all primary studies in trial reports and review articles, and textbooks of anesthesia were searched for other relevant studies. No abstracts or reports of meeting presentations were included; nor was any attempt made to obtain unpublished studies and data. Papers reporting comparative clinical trials of general and locoregional anesthesia were collected for analysis. Only the study design was considered to avoid selection bias.

The chosen articles were then carefully reviewed in order to select comparable trials for analysis. The criteria for inclusion were: 1) a prospective, clinical investigation in humans, retrospective investigations were excluded; 2) the primary intention of the trial had to be the comparative evaluation of general and locoregional anesthesia; and 3) the reproductive outcome (cleavage rate and pregnancy rate) had to be mentioned. The following information was sought and abstracted as available from each report: numbers of patients in groups of general and

locoregional anesthesia; study drugs and their routes of administration and dosages; surgery type; methods of allocation patients to each group; and reproductive outcomes.

Cleavage rate (CR) is defined as the percentage of oocytes successfully inseminated containing two or more cells. Clinical pregnancy is defined as the presence of one or more gestational sacs at ultrasound examination performed approximately 5-6 weeks after transfer. Cleavage rate and clinical pregnancy rate (PR) were considered to be at least one of the end points investigated. Here we used term risk as the possibility of events (occurrence of cleavage and pregnancy). Treatment effect on reproductive outcome in each study was expressed as a relative risk (RR) and odds ratio (OR). All values were presented together with their 95% confidence intervals (CI). The OR of each trial, defined as the odds ratio of CR or PR in the general anesthesia group to the odds of the events in the locoregional anesthesia group, was calculated by dividing the difference between the incidence of general and locoregional anesthesia by the variance of that trial. The RR was defined as the ratio of the proportion of successful trials in locoregional anesthesia group to the proportion of successful trials in the general anesthesia group. The variances and the event rates of individual studies were combined to obtain the pooled ratio. The OR across all studies was calculated by Peto's method. Inclusion of an odds ratio of 1.0 in the CI indicated that the result showed no difference between general and locoregional anesthesia. A fixed model was used to measure effect size. The heterogeneity of combined results was calculated as heterogeneity by chi-square according

to Q Cochran test (8). L'Abbe's graph for approving homogeneity and a comparison of effects was drawn. The computer program EasyMA 97 (9) was applied for the calculation. We tested for homogeneity under the null hypothesis that the relative risks were the same across studies. P-value over 0.05 was interpreted as indicating that the differences in study results were consistent with random variation.

RESULTS

Six prospective studies retrieved from the MEDLINE were selected (10-15). Two studies (10, 11) that were not clearly defined as patients' allocation were excluded. Three studies were randomized and one was a matched, controlled trial (15). Some studies (12, 13) compared general and local anesthesia, others (14, 15) compared regional anesthesia (epidural and paracervical block). Local and regional anesthesia were included in the same category as locoregional anesthetic technique (Table 1). In the general anesthesia group, the main agents were not clearly defined in every study.

The test of heterogeneity by L'Abbe's graph was negative in both event rates of reproductive outcomes (Fig. 1). Consistent effects were also demonstrated. The Q Cochran test for homogeneity of the RR and OR indicated that the studies could be pooled together on the cleavage and pregnancy rates (Table 2 and 3, Fig. 2). In Fig. 1A, marks that indicated event rates were scattered around the line of equality in cleavage overview. The pooled RR was 1.01 (CI 0.95-1.09, $p=1.00$) and risk

Table 1. Anesthetic techniques and drugs used

Author (Ref No.)	General anesthesia	Locoregional anesthesia
Lewin A et al. (12)	Not defined	0.5% bupivacaine 10-15 mL with pethidine (1.5 mg/kg) and diazepam 10 mg (i.v. mix and drip in 100 mL isotonic saline solution)
Lewin A et al. (13)	Not defined	1% lidocaine 5 mL S.Q. with pethidine (50-100 mg) and promethazine 25 mg (i.v. mix and drip in 100 mL 0.9% saline)
Lehtinen A et al. (14)	Fentanyl + N ₂ O	Epidural block (0.33% bupivacaine 12 mL)
Christiaens F et al. (15)	Propofol + air	Paracervical block (mepivacaine 400 mg)

Table 2. Cleavage rate by anesthetic method

Author (Ref No.)	Cleavage rate (%)		Relative risk (95% CI)	Odds ratio (95% CI)	Risk reduction (%)
	General	Local			
Lewin A et al. (12)	63 (15/24)	62 (13/21)	1.01 (0.64-1.59)	1.03 (0.31-3.39)	-1
Lewin A et al. (13)	53 (168/318)	53 (127/240)	1.00 (0.85-1.17)	1.00 (0.71-1.39)	0
Lehtinen A et al. (14)	81 (25/31)	79 (15/19)	1.02 (0.77-1.36)	1.11 (0.27-4.56)	-2
Christiaens F et al. (15)	48 (696/1462)	47 (587/1253)	1.02 (0.94-1.10)	1.03 (0.89-1.20)	-2
Pooled			1.01 (0.95-1.09) $p=1.00$	1.03 (0.90-1.18) $p=1.00$	-1

CI, confidence interval; General, general anesthesia; Local, locoregional anesthesia

Table 3. Pregnancy rate by anesthetic method

Author (Ref No.)	Pregnancy rate (%)		Relative risk (95% CI)	Odds ratio (95% CI)	
	General	Local			
Lewin A et al. (12)	7 (1/15)	8 (1/13)	0.87 (0.08-9.31)	0.86 (0.05-14.63)	13
Lewin A et al. (13)	13 (7/56)	15 (8/55)	0.86 (0.34-2.18)	1.00 (0.28-2.49)	14
Lehtinen A et al. (14)	0 (0/25)	0 (0/15)	0.61 (0.00-150.04)	0.00 (0.00-0.00)	39
Christiaens F et al. (15)	13 (38/283)	19 (49/264)	0.73 (0.49-1.07)	0.68 (0.43-1.08)	27
Pooled			0.75 (0.52-1.06) <i>p</i> =0.99	0.70 (0.47-1.08) <i>p</i> =0.93	25

CI, confidence interval; General, general anesthesia; Local, locoregional anesthesia

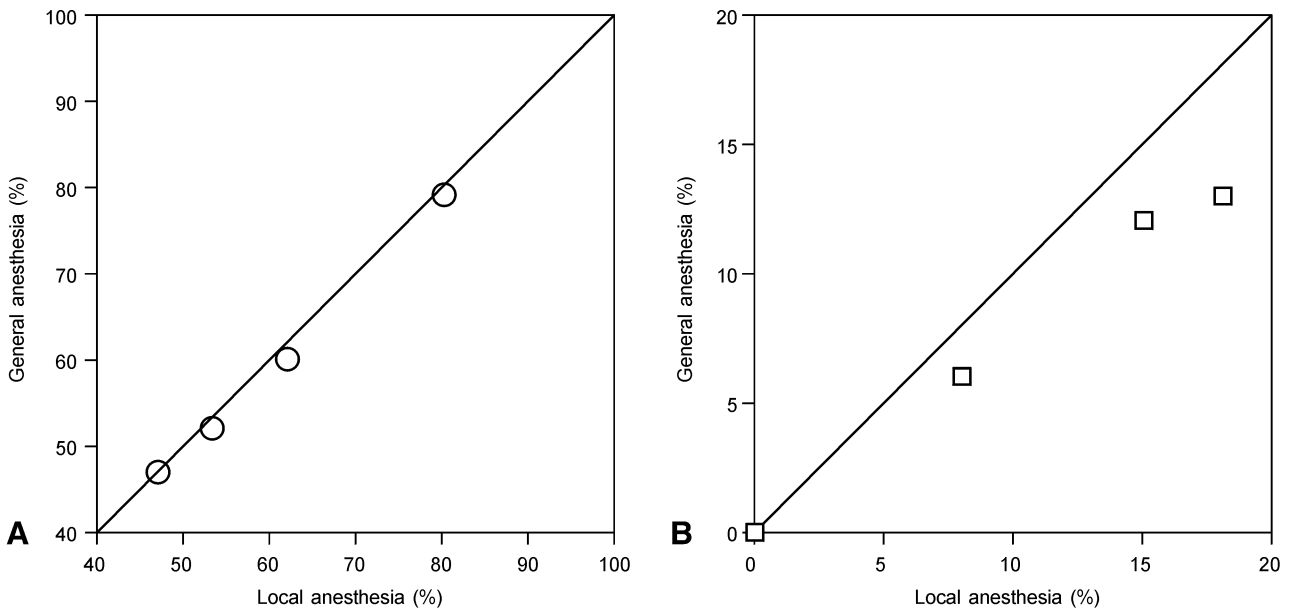


Fig. 1. Event rates of general and local anesthesia (A: Cleavage rates, B: Pregnancy rates). Diagonal line indicates the 'equality' of each event. Local anesthesia means locoregional anesthesia.

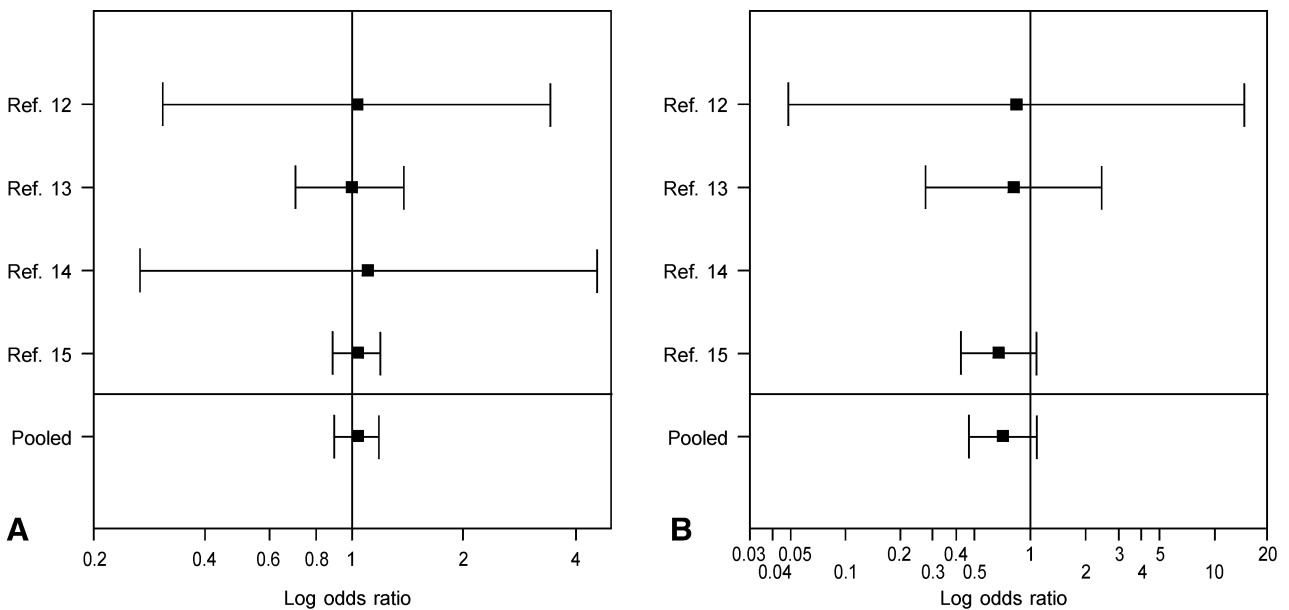


Fig. 2. Odds ratios are plotted on the x-axis as a logarithmic scale (A: Cleavage rates, B: Pregnancy rates). Horizontal line of each trial means an odds ratio with 95% confidence interval.

reduction was -1%. The pregnancy event rates that were consistently below the line of equality implied that the magnitude of effect was reliable (Fig. 1B). This corresponded to a RR for pregnancy of 0.75 (CI 0.52-1.06, $p=0.99$) and 25% risk reduction (CI interval from -6% to 48%) (Table 2 and 3). The pooled OR in both reproductive outcomes were CR 1.03 (CI 0.90-1.18, $p=1.00$) and PR 0.70 (CI 0.47-1.08, $p=0.93$) (Fig. 2). In both reproductive outcomes, 1.0 in CI was inserted to show the differences between the groups, however, the differences were not significant.

DISCUSSION

Despite all the complex procedures of reproductive techniques, the most commonly performed procedure is IVF. Transvaginal ultrasound-guided follicular puncture techniques have become routine in many centers. Oocytes retrieval still requires some form of analgesia or anesthesia. Various techniques of anesthesia have been provided for reproductive technology and some outcome parameters have been reported as results. Among the parameters, only two outcomes (CR and PR) were consistently reported in four studies. To determine whether anesthesia affects IVF, many studies were performed. Reported studies were inconclusive because they either had a small study population or did not control for possible confounding factors such as patient age, study design or duration of the procedure.

Chung et al. (16) investigated the reproductive outcome performed under general and epidural anesthesia. Epidural anesthesia had a significantly higher pregnancy rate for the general anesthesia group in retrospective study. However, Christiaens et al. (15) suggested that there was no significant difference in pregnancy rate by undergoing general anesthesia using propofol or paracervical block in prospectively matched design. Botta et al. (11) also reported no favorable improvement of outcomes in epidural anesthesia for general anesthesia. Timm et al. (22) compared the effects of general anesthesia versus intravenous sedation during ultrasound guided egg retrieval. General anesthesia did not lower fertilization, cleavage, implantation or pregnancy rates. In this meta-analysis, combined results from general anesthesia group showed a 25% reduction in risk, but CI included 0% and 1.0 in OR, indicating that both groups were no different in reproductive outcomes.

Among the many contributing factors to the IVF result, anesthetic agents have been suspected to have deleterious effects in general anesthesia outcomes. Potent inhaled agents, nitrous oxide, propofol and intravenous agents were studied (17-20). An agent was administered

in single or combined form and compared to local anesthetics. Local anesthetics were also analyzed and the concentration of the local anesthetics in follicular fluid was measured. Lidocaine was found in the follicular fluid but did not reduce fertilization or the cleavage rate in paracervical block (21). Belaisch-Allart et al. (10) and Lewin et al. (12) did not find any significant role of anesthetics in the cleavage and pregnancy rate. Recently, a multicenter pilot survey evaluating the effect of propofol, nitrous oxide, midazolam and isoflurane on the clinical pregnancy rate was performed (6). That survey found that a more extensive prospective, randomized study was not warranted because there were no agent-related differences in clinical pregnancy rates. Different conclusions derived from individual studies may result in confounding factors such as applied techniques, patients' characteristics and a different stress response. A large number of trials involved in a prospective study was used as material for meta-analysis, revealing no difference in both general and locoregional anesthesia groups. Sedatives (diazepam) and narcotics (pethidine) were administered in the locoregional anesthesia group, but these agents seemed not to disturb in the RR and OR.

Depending on the available published evidence, no anesthetic technique can be definitively recommended as being more beneficial on reproductive outcome (CR and PR) for IVF procedure requiring analgesia and anesthesia.

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