Optimizing the embryo transfer technique
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Chapter 13

Difficult Embryo Transfer: The Impact of Propofol Anesthesia.

Ahmed M. Abou-Setta, Ragaa T. Mansour, Hesham G. Al-Inany, Gamal I. Serour, Mohamed A. Aboulghar, Mohamed El-Wassify

Abstract

Background: Difficult embryo transfers (ET) requiring general anesthesia are occasionally encountered in clinical practice. Little evidence is present in the literature as to the success rates when compared with difficult transfers not requiring anesthesia. 

Objective: To evaluate the impact of using Propofol anesthesia during difficult embryo transfers on the implantation and clinical pregnancy rates.

Design: Retrospective patient chart review.

Materials and methods: Women undergoing ICSI cycles in the Egyptian IVF-ET center, from January 2000 – December 2002, and having difficult ET requiring general anesthesia (Group I = 99 women) were included. A matching group of women with difficult ET, without anesthesia (Group II = 99 women) were used as a control.

Results: There were no significant differences in the patient demographics (e.g. age, period of infertility, number of oocytes retrieved, fertilization rate, embryo quality, number of embryos transferred. Moreover, there was no significant differences in implantation (Group I = 19.15%, Group II = 20.86%) or clinical pregnancy rates (Group I = 36.36%, Group II = 33.33%).

Conclusion: The use of propofol general anesthesia during difficult embryo transfer does not seem to improve the implantation and pregnancy rates. Even though, prospective randomized trials are needed to confirm these findings.

Key words: Propofol, Embryo transfer, Assisted Reproduction, ICSI, IVF
Introduction
Embryo transfer (ET) is the final step in the IVF/ICSI treatment process. It is also the last step in which clinical manipulation may directly affect the outcome of the assisted reproduction treatment cycle. The majority of patients undergoing IVF/ICSI will reach the transfer stage, with good quality embryos available for transfer, but only a small proportion of them will ever achieve a clinical pregnancy. It is estimated that up to 85% of the embryos replaced into the uterine cavity will fail to implant (1). The pregnancy rate following embryo transfer is generally dependent upon multiple factors including embryo quality, endometrial receptivity and the technique of the embryo transfer itself (2).

One important aspect of the embryo transfer technique that has received limited attention is the use of propofol anesthesia during difficult embryo transfers. Whether Propofol anesthesia during embryo transfer could have a potential impact on conception is not clear from the medical literature. This issue was not even mentioned as an important variable that might affect the outcome of embryo transfer in two recent reviews of the literature (2, 3). Even so, it is clear from a recent systematic review and meta-analysis that difficult embryo transfer is associated with a significant drop in implantation rate when compared to ‘easy’ transfers (O.R = 0.64, 95% CI = 0.52 – 0.77) (4).

In the medical literature, there is conflicting evidence on the impact of different anesthetic agents used during oocyte retrieval on pregnancy rates following embryo transfer (5 – 8). Moreover, only a few studies have discussed the impact of general anesthesia during the embryo transfer procedure on the implantation and clinical pregnancy rates (9 – 11). In a previous work by our group, there was no adverse or beneficial effect of propofol anaesthesia on both implantation and pregnancy rate in women with easy embryo transfer (12). Therefore in the present study, we wished to evaluate the possible beneficial or detrimental effect of using propofol anesthesia on IVF-ET outcome in patients undergoing a difficult embryo transfer.
Materials and Methods
Data obtained from clinical records of subfertile couples undergoing embryo transfer under general anesthesia over a two-year period were obtained and analyzed. The inclusion criteria were: female age < 39 years old, with normal hormonal profile and no pelvic pathology, and no surgically retrieved sperms. Inclusion criteria were difficultly in cannulating the cervix encountered during embryo transfer with clinician preference of using general Propofol anesthesia. Patients undergoing ICSI in the same period of time with the same inclusion criteria and which did not have general anesthesia for ET were selected as a control group.

All participants received the GnRHa long protocol, 0.1mg/day (Decapeptyl, Ferring Pharmaceuticals) starting on day 20 of the cycle till the day of hCG injection. After down regulation was confirmed, 150 – 300 I.U of hMG/day was started for 7 days; then the dose was adjusted according to the ovarian response as measured by serum estradiol levels and ultrasound monitoring. Ten thousand international units of hCG (Pregnyl; Nile Co., Cairo, Egypt) were given I.M. when two or more follicles reached ~18 mm in mean diameter. Ovum retrieval using transvaginal ultrasound was scheduled 36 hours after hCG injection. All participants were enrolled in our ICSI program, which is described elsewhere (13).

None of the patients in either group received premedication prior to the embryo transfer. In the anaesthesia group, a 22-gauge catheter was inserted in one arm, ECG (lead II) was connected and blood pressure and pulse oximetry were instituted. Induction of general anaesthesia consisted of pre-oxygenation by face mask, followed by intravenous bolus of 2 mg/kg propofol (Diprivan®; Zeneca, Manchester, UK) as an induction dose and anaesthesia was maintained by inhalation of isoflurane 1.5% and oxygen 100% through a face mask. Embryo transfer was performed according to the standard procedure used in our center (14). In general, embryo transfer was performed 48–72 h after oocyte pick-up using the Wallace catheter (H.G.Wallace Ltd, West Sussex, UK). In both groups, the embryo transfer was done at the lithotomy position. The previously taken ultrasound picture of the uterus and dummy embryo transfer (Mansour et al., 1990) were revised to get an idea of the length and direction of the uterine cavity. After performing the dummy embryo transfer, the embryos were loaded into
a new catheter, either Wallace or Cook according to the dummy embryo transfer as follows. The embryo transfer catheter was rinsed then filled with tissue culture medium. About 10–20 ml tissue culture medium was aspirated, then the embryos (up to three) were aspirated in 10–20 ml tissue culture medium so that the embryos would be away from the tip of the catheter. If the Wallace catheter was used, the soft internal catheter, protruding from the external rigid sheath, was introduced gently through the internal cervical os and stopped 1 cm below the fundus. The outer rigid sheath was stopped just at the internal cervical os and not pushed beyond it. If the Cook catheter was used, the tip of the inner catheter was positioned flush with the external sheath until it passed the internal cervical os, then the internal sheath one was advanced 2 cm into the uterine cavity.

Luteal phase support was given routinely in the form of a daily progesterone injection (100 mg, progesterone; Steris, Phoenix, AZ, USA). A serum β-hCG test was done to confirm pregnancy two weeks after the embryo transfer. Clinical pregnancy was diagnosed 3 weeks after a positive test by the presence of a gestational sac with fetal echoes and pulsations on ultrasound.

The primary outcome measures for this study was the odds of a clinical pregnancy and embryo implantation following Propofol anesthesia compared to no anesthesia.

**Statistical evaluation**

Data are presented as mean ± SD. Different outcome measures were compared using Student's t-test, $X^2$ or Fisher's exact test where appropriate. Odds ratios (using the Woolf (Logit) method), 95% confidence intervals and P-values are presented. A P-value of <0.05 was considered to be significant. Statistic analysis was performed using Arcus Quickstat BioMedical (Version 1.0).
Results
The present study enrolled 198 women who had completed an IVF/ET cycle, and divided into two groups: Group I (99 women who had difficult embryo transfer under general anesthesia), and Group II (99 women who had difficult embryo transfer without general anesthesia). There was no statistically significant difference in the age, infertility duration, number of oocytes retrieved, fertilization rate or embryos obtained between both groups (Table I).
In addition, there was no statistically significant difference between both groups regarding clinical pregnancy (Group I = 36/99 versus Group II = 33/99; O.R = 1.14, 95% CI = 0.64 to 2.05; P = 0.77) or implantation rates (Group I = 54/282 versus Group II = 58/278; O.R = 0.89, 95% CI = 0.59 to 1.36; P = 0.69).
Discussion

Embryo transfer is the final and most crucial step in IVF. Patients experiencing difficult embryo transfer are not uncommon in daily practice, especially in large infertility centers. In general, difficulty in threading the cervix occurs in about ~5% of all embryo transfers (15). Several techniques have been discussed as ways of bypassing the unrelenting cervix. These include the use of cervical dilatation, using dilators (16) or hygroscopic rods (17), cervical shaving to widen the cervical canal in cases of cervical stenosis (18) and the use of instrumental assistance during the embryo transfer such as tenaculum, sounding or dilatation. As a last resort, some authors prefer to use transmyometrial embryo transfer to deposit the embryos in the uterine cavity (19).

Even though these techniques may assist the clinician in reaching the endometrial cavity, they also carry associated risks, including stimulating uterine contractions, cervical and endometrial injuries and lacerations, increase in the presence of blood on the catheter tip and cervix, and most importantly, cumulatively a decrease in clinical pregnancy and implantation rates (20).

Propofol (Diprivan®) is an intravenous sedative-hypnotic drug widely used as a sole anesthetic agent in minor interventions, such as ovum pick up, cervical dilatation and minor intrauterine procedures. Propofol (2,6-diisopropylphenol) is an alkylphenol that has a rapid onset of action and recovery. In addition, Propofol exerts smooth muscle relaxation, a mechanism that may involve IP3-induced SR Ca2+ release in calcium signaling pathways.

Propofol acts as a hypnotic and can be used as both an induction agent and/ or as maintenance anesthetic. A three compartment linear model, characterizes Propofol’s pharmacokinetics, with fast distribution into the tissues, rapid metabolic clearance, and a slow return to the peripheral compartment. Following the initial bolus dose, propofol equilibrates between the plasma and the brain. Plasma levels, however, decline quickly as a result of high metabolic clearance and prompt distribution to the tissues. These properties account for Propofol’s rapid onset and short duration of action. Distribution time decreases as tissues equilibrate with plasma and become saturated. Elimination is triphasic; with the distribution half-life being 2 – 10 minutes; the second phase half-life being 21 – 56 minutes; and the terminal elimination half-life 1.5
to almost 30 hours. The last phase is not thought to be clinically significant. Mean induction time is 30 to 40 seconds after a 2.0 to 2.5 mg/kg bolus. Discontinuation of propofol anesthesia usually results in a rapid decrease in plasma concentrations and prompt awakening. Propofol has a clearance rate of 23-50 ml/kg/minute. The presence of hepatic cirrhosis or renal insufficiency does not appear to significantly alter its pharmacokinetics (21).

To overcome the limitations of retrospective analysis, both groups (with and without anesthesia) were matching regarding age, duration of infertility, number of oocytes retrieved, fertilization rates and number of embryos transferred. The participants of the control group were only recruited during the same period of time in order to guarantee that the lab conditions were the same.

Despite controversial reports with regard to the influence of propofol anesthesia on implantation rates and clinical pregnancy rates in humans (22 – 25). The previous studies investigated the impact of propofol used during ovum pickup, or Gamete Intra-fallopian Transfer (GIFT), or during ‘easy’ embryo transfer on pregnancy rate and implantation rates. To the best of our knowledge this is the first study to determine the beneficial or detrimental effect of Propofol anesthesia during difficult embryo transfers and it confirms our previous work (12).

In the present study, there was no statistically significant difference in implantation, or clinical pregnancy rates. This concludes that there is no evidence from our data that the administration of propofol during the procedure of embryo transfer had a negative impact on the embryos as measured by probability of a clinical pregnancy or implantation rates. Therefore, Propofol anesthesia may offer clinicians a complementary measure while dealing with a difficult embryo transfer. Even so adequately powered randomized controlled trials are needed to confirm our findings.
References
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Table 1. Demographic and cycle characteristics of the Propofol anesthesia and no anesthesia groups.

<table>
<thead>
<tr>
<th></th>
<th>Anesthesia (Mean ± SD)</th>
<th>No Anesthesia (Mean ± SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>32.02 ± 4.07</td>
<td>31.13 ± 4.68</td>
<td>P = 0.78</td>
</tr>
<tr>
<td><strong>Infertility</strong></td>
<td>8.99 ± 3.44</td>
<td>5.95 ± 3.72</td>
<td>P = 0.14</td>
</tr>
<tr>
<td><strong>Oocytes</strong></td>
<td>13.37 ± 7.32</td>
<td>12.12 ± 6.95</td>
<td>P = 0.32</td>
</tr>
<tr>
<td><strong>PB</strong></td>
<td>10.86 ± 5.77</td>
<td>8.77 ± 5.26</td>
<td>P = 0.75</td>
</tr>
<tr>
<td><strong>2PN</strong></td>
<td>7.01 ± 4.32</td>
<td>5.45 ± 3.53</td>
<td>P = 0.91</td>
</tr>
<tr>
<td><strong>Cryopreserved Embryos</strong></td>
<td>2.51 ± 3.56</td>
<td>1.62 ± 3.16</td>
<td>P = 0.69</td>
</tr>
<tr>
<td><strong>Embryos Transferred</strong></td>
<td>3.13 ± 0.92</td>
<td>2.85 ± 0.79</td>
<td>P = 0.58</td>
</tr>
<tr>
<td><strong>High Quality Embryos (G1)</strong></td>
<td>2.38 ± 0.93</td>
<td>1.95 ± 0.88</td>
<td>P = 0.74</td>
</tr>
<tr>
<td><strong>Good Quality Embryos (G2)</strong></td>
<td>2.47 ± 1.13</td>
<td>2.23 ± 0.86</td>
<td>P = 0.42</td>
</tr>
<tr>
<td><strong>Fair Quality Embryos (G3)</strong></td>
<td>1.54 ± 0.66</td>
<td>1.33 ± 0.62</td>
<td>P = 0.54</td>
</tr>
<tr>
<td><strong>Fertilization Rate</strong></td>
<td>62.21%</td>
<td>64.42%</td>
<td>P = 0.37</td>
</tr>
<tr>
<td><strong>Pregnancy Rate</strong></td>
<td>36.36%</td>
<td>33.33%</td>
<td>P = 0.77</td>
</tr>
<tr>
<td><strong>Implantation Rate</strong></td>
<td>19.15%</td>
<td>20.86%</td>
<td>P = 0.69</td>
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