Anaesthetic implications of 32% Dextran-70 (Hyskon®) during hysteroscopy: hysteroscopy syndrome

Devanand Mangar MD

This review describes the properties and side effects of Hyskon® and the implications for the patient and anaesthetist during hysteroscopy. The amount of Hyskon® absorbed is dependent on the injection pressure, the extent of tissue trauma, the seal of the hysteroscope around the cervix, and the duration of infusion. The mechanism of pulmonary oedema after absorption of Hyskon® is fluid overload, and not injury to pulmonary capillary endothelium. The haematological effects are primarily due to haemodilution. However, case reports suggest that Dextran 70 may cause a syndrome resembling disseminated intravascular coagulation. The allergic response to Hyskon® consists of both an anaphylactic and an anaphylactoid component. It is recommended that hysteroscopy with Hyskon® be limited to 45 min, and that all possible measures be taken to minimize tissue trauma and bleeding. The volume of Hyskon® should be limited to less than 500 ml, since pulmonary oedema and coagulopathy have been described with even lesser amounts. The cumulative volume of Hyskon® should be monitored frequently and the patient should be closely monitored for signs of impending pulmonary oedema.

Cet article décrit les propriétés et les effets secondaires de l'Hyskon® et les implications pour le patient et l'anesthésiste pendant l'hystérocopie. La quantité d'Hyskon absorbée dépend de la pression d'injection, de l'extension du traumatisme

Key words

COMPLICATIONS: pulmonary oedema;
SURGERY: gynaecological, hysteroscopy;
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From the Department of Anesthesiology, University of South Florida College of Medicine, Tampa, Florida.

Address correspondence to: Dr. D. Mangar, University of South Florida College of Medicine, Department of Anesthesiology, 12901 Bruce B. Downs Blvd., Box 59, Tampa, FL 33612

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tissulaire, de l'étanchéité de l'hystérocopie inséré dans le col et de la durée de la perfusion. Le mécanisme de l'oedème pulmonaire après la résorption d'Hyskon est une surcharge liquidienne et non une lésion endothéliale des capillaires pulmonaires. Les effets hématologiques sont d'abord dus à l'hémomodilution bien que des rapports de cas suggèrent que le dextran 70 peut causer d'emblée une coagulation intravasculaire disséminée. La réponse allergique à l'Hyskon comporte à la fois un versant anaphylactique et anaphylactoid. On recommande que l'hystérocopie à l'Hyskon soit limitée à 45 minutes et que soient pris tous les moyens possibles pour diminuer le traumatisme tissulaire et le saignement. Le volume d'Hyskon doit être limité à moins de 500 ml puisque l'oedème pulmonaire et la coagulopathie ont été même décrits pour des quantités moindres. La quantité perfusée d'Hyskon devrait être régulièrement comptabilisée et le patient devrait être étroitement monitorisé quant aux signes précurseurs d'oedème pulmonaire.

Modifications in hysteroscopic technique including improvements in optics, light delivery systems and anaesthesia, have made it a safer procedure.¹ Visualization during hysteroscopy is facilitated by irrigation with Hyskon® (32% Dextran-70, Hyskon® Division, Pharmacia, Piscataway, New Jersey) a clear, viscid, sterile, nonpyrogenic solution of Dextran-70 (32% W/V) in dextrose (10% W/V). Hyskon® is nonelectrolytic, enabling its use in laser and diathermy surgery. Hyskon® is indicated for use with the hysteroscope as an aid in distending the uterine cavity and in irrigating and visualizing its surfaces. However, use of Hyskon® is not without problems. Cases of pulmonary oedema, coagulopathy, and anaphylaxis have been reported due to the rapid intravascular absorption of Hyskon®.²⁻¹⁰

If too much Hyskon® is absorbed or injected into the circulation, a condition resembling the transurethral prostatectomy (TURP) syndrome may develop. In this review the properties and side effects of Hyskon® and the implications for the patient and anaesthetist during hysteroscopy are described. Recommendations for its safe use are made.

Hysteroscopy and distending medium

Hysteroscopy, first introduced in 1869 by Pantaleoni,¹¹ is an established, and relatively safe gynaecological procedure for visual and instrumental inspection of the uterine cavity.¹² The panoramic operating hysteroscope is inserted through the cervix to view the endometrium for diagnostic and therapeutic procedures. Besides Hyskon®, other liquids including 0.9% sodium chloride, 3% sorbitol, and carbon dioxide have been used as the distending medium.

Carbon dioxide is sometimes preferred to Hyskon® as a distending medium for diagnostic hysteroscopy because of its low index of refraction, which allows wide-angle viewing and good quality photographic recording. However, carbon dioxide may cause foaming when blood is present, which reduces the field of vision during the procedure. It also has been reported to cause air emboli, hypercarbia, and acidosis.

Dextran 70 has been used as a distending medium for hysteroscopy since 1970.¹³ The major advantages of Dextran 70 are its excellent optical qualities and its high viscosity, which prevents it from mixing with blood and makes it ideal during procedures in which bleeding is common.

Resection of space-occupying lesions, such as submucous myomas have been described using Hyskon®.¹⁴⁻¹⁵ The gynaecologist usually performs simultaneous laparoscopy and hysteroscopy to remove Hyskon® from the peritoneal cavity and to rule out uterine perforation.

An electrical pump has been proposed for Hyskon® infusion because the high viscosity makes Hyskon® difficult to handle and adequate infusion rates difficult to obtain.¹ Distension of the uterus and separation of the uterine walls require a pressure of at least 10 cm H₂O.¹ Fluid will pass through the fallopian tubes and appear in the cul-de-sac, when intrauterine pressures exceed 50 cm H₂O. We have measured intrauterine pressures of 10 to 160 mmHg, and manual injection pressures of 0.5 and 3.9 atmos during routine manual injection of Hyskon®.¹⁶ The high pressure may result in continuous injection of the distending medium from the uterine cavity into the circulation. High serum levels of Hyskon® in excess of 1000 mg · dl⁻¹, have been demonstrated 30 min after intrauterine infusion of at least 300 ml of Hyskon®. This corresponds to an absorbed volume of up to 211 ml of Hyskon®. The amount absorbed is dependent on the injection pressure, the tissue trauma, the seal of the hysteroscope around the cervix, and the duration of infusion.

Potential complications

Pulmonary oedema

Pulmonary oedema has been reported with Hyskon®

infusion volumes ranging from 150 to 1200 ml.²⁻¹⁰ This is believed to result from intravascular absorption. Forty-two laser hysteroscopies were completed at SUNY-HSC, Syracuse, New York in 1988 and Hyskon® was used in 22 of these. The mean dose $\pm$ SD was 480 ml $\pm$ 236 ml. One patient in whom 600 ml of Hyskon® was used, developed pulmonary oedema as evidenced by postoperative hypoxia requiring supplemental oxygen and furosemide. Two others were given furosemide prophylactically to induce diuresis and avoid fluid overload.³ Although noncardiogenic drug-related pulmonary oedema has been described after administration of methadone,¹⁷ heroin,¹⁸ salicylates,¹⁹ and Dextran 40,²⁰ the pulmonary oedema associated with Hyskon® was previously considered to be noncardiogenic.^{2,3,5,6} Lukacsko reported that volumes of Hyskon® >500 ml given *iv* cause pulmonary oedema secondary to increases in plasma volume.⁷

Pulmonary oedema after Dextran 40 was first reported in a trauma victim who had been receiving Dextran 40, 2000 mg per day for suspected phlebitis.² The authors concluded that the pulmonary oedema was not cardiogenic because there were no abnormal auscultatory findings, ECG or enzyme changes. It was postulated that dextran had a direct toxic effect upon the pulmonary capillaries similar to that described after methadone.¹⁷ In several reports, noncardiogenic pulmonary oedema of similar origin has been suspected after 300-900 ml of Hyskon®.^{2,3,5,6} However, fluid overload cannot be ruled out since invasive monitoring was not used because of the presence of a coagulopathy.⁷ Two cases of pulmonary oedema were described after 800 ml and 700 ml of Hyskon® in patients with invasive haemodynamic monitoring.⁹⁻¹⁰ In these patients pulmonary artery catheter measurements showed a PAOP of 22 and 21 mmHg from which the authors concluded fluid overload. Schinagel⁴ suggested that the effect of Hyskon® may be physical rather than chemical, and the pulmonary oedema should respond to measures directed to remove the excess intravascular volume. He recommended phlebotomy and, in severe cases complicated by renal failure unresponsive to diuretics, plasmapheresis to remove the extra dextran, as suggested by Moran *et al.*²¹

Hyskon® is hyperosmotic: 100 ml of Hyskon® expands plasma volume by 860 ml.⁷ In previous studies we found a plasma concentration of Hyskon® of 2900 mg · dl⁻¹ corresponded to an absorbed volume of 227 ml, which would expand plasma volume by 1952 ml.¹⁶

The use of no more than 500 ml of Hyskon® has been recommended and arbitrarily set by the manufacturer. No correlation has been demonstrated between the amount used with serum concentration or the incidence of coagulopathy or pulmonary oedema. Hyskon® appears to be absorbed in a manner similar to fluids which are absorbed during transurethral prostatectomy when the vascular bed

is open to the irrigating fluid. However, during hysteroscopy, extremely high pressures are used for irrigation, resulting in intravascular absorption. Each patient's requirement for Hyskon® varies depending on the size of the uterus and the extent of the surgery.

Postoperative pleural effusion has been reported after dextran was instilled intraperitoneally to prevent adhesions.²³⁻²⁴ It was postulated that the fluid reached the pleural space as in Meigs syndrome, via a defect in the diaphragm. The pleural effusions in these patients were small, asymptomatic, and disappeared within two weeks.²³

Haematological effects

Dextran 40 has been widely used to prevent thromboembolic disease especially in the high-risk surgical patient. Platelet adhesiveness is decreased secondary to dextran's adherence to the cell membranes of the vascular endothelium and platelets. It causes a depression of platelet factor 3 in normal people.²⁰ Dextran alters the fibrin clot structure making it more susceptible to lysis. Haemodilution of clotting factors exerts an antithrombotic effect, decreased blood viscosity and vascular stasis, and surface coating of erythrocytes which result in decreased erythrocyte aggregation.²²

Intraperitoneal Dextran 70 was shown in a three-day study period to decrease haematocrit secondary to haemodilution, without change in serum electrolyte concentrations, prothrombin time, partial thromboplastin time or platelet count.²⁵ However, clinical case reports²⁻¹⁰ indicate a bleeding pattern similar to disseminated intravascular coagulation. This may be due to dilution²⁶ of the clotting factors or to a direct effect of high concentrations of Dextran 70 similar to those of Dextran 40.

Dextran 40 and 70 are excreted mainly in the urine in unaltered form. The larger molecules of either of these dextrans are taken up by the reticuloendothelial system and by the enzyme dextranase metabolized to carbon dioxide and water.^{22,27-28} It is possible that Dextran 70 is broken down to molecules of smaller size which then produce side effects similar to those seen during infusion of Dextran 40. These side effects include factitious elevations in blood glucose concentration,²² abnormal total protein, abnormal bilirubin, error in blood cross-matching, decreased platelet adhesiveness,²⁹⁻³⁰ renal failure,³¹⁻³² and decreased plasma concentration of fibrinogen and factors V, VIII, and IX.²⁰ These side effects may be in addition to those caused by Hyskon® itself.

Allergic reactions

The increasing use of polysaccharide plasma expanders, such as dextran, has made clinicians more aware of their antigenicity and potential to cause allergic reactions. Dextran was developed as a product of the polymerization of glucose by the bacterium *Leuconostoc mesenteroides* on

sucrose. Patients become exposed to dextrans in many ways. For instance, commercial sugar is frequently contaminated with dextran. Another method of sensitization is through cross reactivity of antibodies directed against polysaccharides of such bacteria as group-H streptococci, pneumococci types II, XII, and XX, and salmonella typhosa.²⁰ Severe anaphylaxis developed in a patient after the administration of 6% Dextran 75, and was found to exhibit significant wheal and erythema skin sensitivity reactivity to type VII pneumococcus polysaccharide (from previous episodes of pneumonia).³³ The reported incidence of anaphylaxis to dextran is approximately 1:10,000.

The overall frequency of anaphylactoid reaction in patients receiving Dextran 70 to prevent thromboembolism in major surgical procedures is 1 in 383, and the incidence of a severe reaction is 1 in 821 in 5745 patients studied.³⁴ These investigators advised against routine administration of Dextran 70 since the risk of Dextran 70 treatment exceeded the risk of thromboembolism.³⁴

Ahmed *et al.*³⁵ reported three cases of severe anaphylactic reaction after using Hyskon® during hysteroscopy. The reaction occurred about ten minutes after exposure of 20 to 75 ml of intrauterine dextran. Although two of the patients were tested for allergies against dextran and found to be negative, the authors³⁵ were unable to explain the profound cardiovascular collapse other than by an allergic response to dextran. Taylor *et al.*³⁶ described a case of generalized itching and a maculopapular rash over the face, chest, and lower arms 30 min after 150 ml of dextran. There was no dyspnoea or hypotension, and the patient responded to steroids and phenergan. Skin testing was not performed because the reaction was negative in patients who had experienced such reactions.³⁷

Prevention of complications

It has been recommended (Pharmacia, personal communication, July 1990) that the maximal dose of Hyskon® should not exceed 500 ml. However, there is no published correlation between the amount of Hyskon® used and its blood concentration. We found that intrauterine Hyskon® absorption and/or injection occur during hysteroscopy after volumes as little as 50 to 100 ml.¹⁶ Serum concentrations were higher with higher amounts of Hyskon® used in ablative procedures. In cases in which extensive ablative procedures are necessary, we suggest that a two-stage procedure be considered. The injection pressures should be low to minimize the amount of intravascular injection. Because of the hypertonicity of Hyskon®, intravascular volume expansion may be greater than that seen during transurethral prostatectomy (TURP) when another irrigant is used. Cleary *et al.*³⁸ observed ascites two days after intraperitoneal instillation of 250 ml Hyskon®, but no dextran was found in the serum for the first 24 hr.

To avoid possible complications with Hyskon® during hysteroscopy³⁹ the amount of Hyskon® used should be noted continuously, and one should be alert to signs of impending pulmonary oedema: rales, increase in peak inspiratory airway pressures, tachycardia and decreased arterial blood haemoglobin saturation. Extensive endometrial ablation is sometimes necessary in young women with menorrhagia and depressed myocardial function from valvular heart disease. In these patients with prosthetic heart valves taking anticoagulants, intraoperative arterial and pulmonary arterial catheter monitoring may be necessary to avoid fluid overload if Hyskon® is used.

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