ORIGINAL RESEARCH PAPER

Volume-7 | Issue-8 | August-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

THE UTILITY OF DEXTRAN AND ITS RELATED COMPLICATIONS IN MICROSURGICAL RECONSTRUCTION: A PROSPECTIVE RANDOMIZED ANALYSIS

Plastic Surgery

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ABSTRACT

Introduction: A study was designed to assess the benefits of low molecular weight dextran and its related complications in microsurgical reconstructions.

Materials & Methods: 20 consecutive patients undergoing microvascular reconstruction during a 1 year period were randomized into two groups. In the First group dextran-40 was administered in the postoperative period according to a standard protocol while the second group was not administered dextran. Flap outcome (survival of the flap) and the incidence of local and systemic complications were evaluated as the other outcome variables in the treatment groups.

Results and Discussion : Both the groups consisted of similar patient profile and type of flaps. The occurrences of local and systemic complications were similar in the both groups and no additional benefit or complications. The present study prospectively demonstrates no significance in addition of low molecular weight dextran in the intraoperative or postoperative scenario of microvascular reconstructions.

KEYWORDS

Thromboprophylaxis, Low Molecular Weight Dextran, Vascular Anastomosis

Introduction

Microsurgery has over the last decade grown leaps and bounds and has been associated with high success rate in recent times. However, a significant number of failures occur even in the hand of the most skilled. Anastomotic occlusion by a thrombus is still the most common cause of failure of these free flaps [(1)]. In view of the prevalence of the local and systemic factors of thrombogenicity, many still consider thromboprophylaxis essential, for the success of this kind of surgery. The most commonly used drugs for post-surgical thromboprophylaxis are heparin and dextran. Numerous studies evaluating prophylactic anticoagulation in microsurgery report efficacy in animal models, however, limited human data exist to support any clinician's preferred method.

Review of Literature: The use of prophylactic antithrombotic agents is the most common strategy for avoiding vascular thrombosis after free flap surgery or vascular repair. As early as 1978, Ketchman proposed that to increase patency rates of microvascular repairs surgeons need agents that (a) decrease platelet function (eg, aspirin), (b) increase blood flow or decrease blood viscosity (eg, dextran), and (c) counteract the effects of thrombin on platelets and fibrinogen (eg, heparin) [(2)].

Dextran is rheomacrodex, a glucose derivative, with an average molecular weight of 70.000 (20,000-40,000 Daltons). The commonly used sterilized solution for clinical use is normal saline and dextran solution, with each bottle containing 500ml with 10% w/v dextran with specific gravity similar to that of plasma and pH is about 7.3 to 7.4 [(3)]. Although used for its thrombus preventing capability, dextran can manifest adverse reactions, such as anaphylactoid reactions, adult respiratory distress syndrome, cardiac overload, hemorrhage, and renal damage. [(4)(5)(6)].

Although a wide variety of regimens for the administration of dextran in the perioperative period have been advocated, two are commonly followed. Johnson and Barker recommend a 40-mL loading dose of dextran 40 before the release of clamps, followed by a 25-mL/hr infusion for 5 days; Buckley and colleagues recommend 500mL of dextran 40 before anastomosis and then 500mL per 24-hour period for 3 days. Conrad and Adams, studying pharmacologic optimization in microsurgery, recommended haemodilution (in particular with dextran 0.4 ml/kg/hour weaned off by postoperative day 5, as ideal thromboprophylaxis [(7)]. But with the prevalent usage, there have been an increasing number of reports of significant morbidity related to low-molecular-weight dextran and many have started questioning its routine use in microsurgery [(8,9,10)]. Adverse reactions to dextran range from a rash to anaphylactic shock. Dextran anaphylaxis is a well-described clinical entity characterized by cutaneous symptoms (usually flushing or urticaria), fever/chills, pulmonary compromise, and hypotension. Serious complications associated with its use have been reported in the literature, including volume overload (osmotic complications), pulmonary edema, cerebral edema, or platelet dysfunction, bleeding diatheses in children, and anaphylaxis with fatal outcome [(9,10,11)]. Paul et al, conducted a large-scale prospective study of dextran-induced anaphylactoid reactions in 5745 patients [(12)]. Dextran induced adult respiratory distress syndrome was another major cause leading to accidental prolonged ventilator dependence. Hein et al. and Taylor et al. both reported cases of non-cardiogenic pulmonary edema after intravenous infusion of dextran [(13,14)].

An uncommon but major complication of dextran's osmotic effect is acute renal failure. Close to 70% of Dextran-40 is excreted in the urine within the first 24 hours after intravenous infusion and the remaining 30% is retained for several more days, prolonging its effects [(15,16)]. Brooks et al recommended avoiding dextran therapy in patients with chronic renal insufficiency and a creatinine clearance rate of less than 40 mL/min [(17)].

A prospective study of Dextan-40 related utility and complications was conducted in a tertiary care centre over 20 microsurgical cases. This study would suggest utility of Dextran-40 and also suggest the scope of dextran related complications in microsurgical cases.

Materials and methods

A total of 20 patients, operated at a single centre by the same team of reconstructive surgeons, were included in this study. The patients, who had a history of anaphylaxis to any drug or bleeding diathesis, were excluded in this study. A detailed consent was obtained from the patients after explaining the limbs of the study and risks.

All the above patients, in both the groups, received an intraoperative bolus of 5000 IU heparin, 10 minutes before flap pedicle ligation.

These 20 patients were assigned rapidly into two groups by a simple randomization technique of alternating patients sequentially; with the first patient being in group one at the start of the study.

Group I – All the patients in this group received dextran- 40 cc per hour for 120 hours of immediate postoperative period or till any complications arose.

Group II – All the patients in this group did not receive postoperative administration of dextran-40.

Postoperatively, the antibiotic cover and fluid requirement were administered similarly with a matching rate to the weight and requirements of the patient.

A descriptive proforma was utilized in assessing the patient demographics and the outcome variables.

The assessment variables were
a) Haematoma (postoperative)
b) Intraoperative blood loss
c) Seroma
d) Drain volume
e) Partial or complete flap loss
f) Systemic complications – congestive cardiac failure, pleural effusion and pneumonia

Meticulous records were maintained. It was advised to stop the administration of dextran, in case of occurrence of severe systemic complication or development of flap necrosis.

RESULTS

1) Age distribution:

The patients were predominantly in the middle aged (mean-42.55yrs) and a majority of 65% were in the higher age group. There was only one patient of pediatric age group.

The age of the patient is a pertinent factor as with increasing age, the associated co- morbidities are generally in increase and risk of thrombosis and complications have an increased tendency to occur.

In this study, however, there was no statistically significant difference in the functional outcomes in different age group.

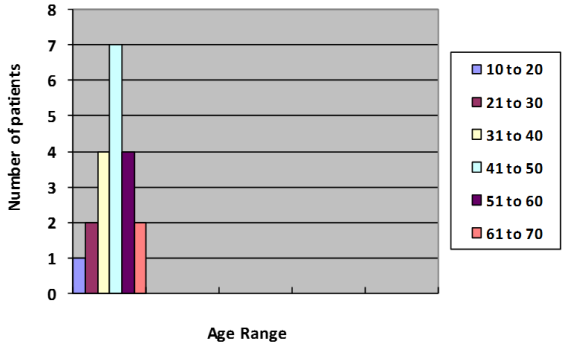
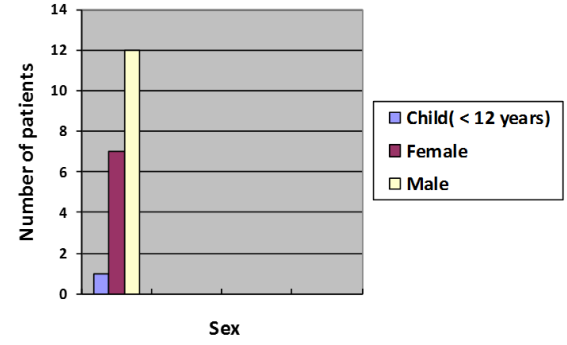


Figure 1: Age distribution of the patients

Gender Distribution: (Fig 2)

Males were predominant (60%) in this study and also formed the majority group in Group I (those that were administered dextran in the postoperative period).

The complication of partial loss of the flap and also another of the loss of skin paddle were both seen in a male. The habit of tobacco consumption (chewable or smoking) was also prevalent more in males. Comorbid disabilities like hypertension and diabetes too were prevalent more in males than females.



Type of flaps in each group: (Fig 3)

There was near equal distribution of cases in each group of the study with all types of free flaps namely, fasciocutaneous (Anterolateral thigh flap & Radial forearm flap), myocutaneous flap (Lattismus Dorsi and Rectus Abdominis myocutaneous flap) and Osteocutaneous flap (free fibula flap). Hence type of flap was not a confounding factor in this study and the entire study was performed by single team.

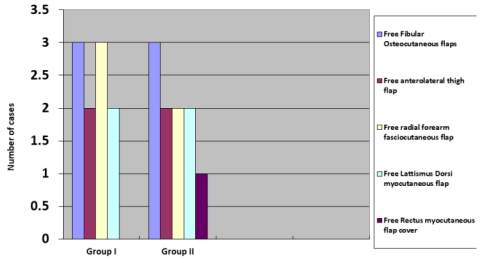


Fig 3: Types of Free Flaps in the two Groups

Aetiology of defects for reconstruction –

The post oncological resection defects were the majority defects (50%) whereas post traumatic defects formed 45% of the total reconstructions.

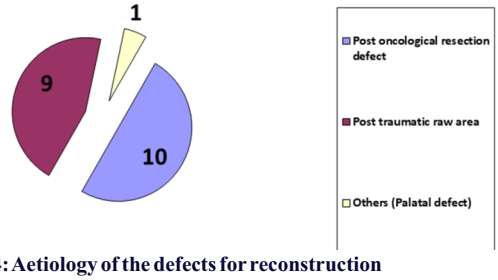


Fig 4: Aetiology of the defects for reconstruction

2) Complications

a. Flap Loss

Group I (with dextran)	Group II (without dextran)
One case of partial loss of anterolateral thigh flap	One case of complete loss of free fibula flap
	One case of only skin paddle of the fibular Osteocutaneous flap loss

b. Pedicle thrombosis

Group I (with dextran)	Group II (without dextran)
One case of anterolateral thigh flap was seen with pedicle thrombosis (seen during re-exploration)	No cases of pedicle thrombosis were seen

Pedicle thrombosis was initially suspected by clinical diagnosis of failing flap in the initial post-operative period during flap monitoring and hence was taken up for re-exploration. The flap survived after the exploration.

c. Hematoma

This is the incidence of sub flap or donor site hematoma, which was seen in 2 cases in Group I (with dextran 40) and in one case in Group II.

Group I (with dextran)	Group II (without dextran)
In a case of free radial forearm flap, donor site hematoma formation occurred. This lead to local swelling and loss of graft applied. Drainage and secondary grafting was done.	A case of free fibula graft developed subflap hematoma noticed in 48 hrs. A re-exploration on 3rd postoperative day (per op - no obvious cause of the bleed seen). The hematoma was evacuated to relieve pressure over the pedicle but eventually the flap was lost.
The second case was that of a case of anterolateral thigh flap which had subflap haematoma which was relieved by suture removal and evacuation and the flap survived	

d. Drain Average output

The mean output in the either group was similar with the donor site of the Lattismus dorsi flap revealing comparable highest output in either group while the other flaps too had similar output from their flap site drains and donor site drains in comparison during the first 72 hours.

	Group I (with dextran)	Group II (without dextran)
First 24 hours	100 ml	100 ml
Next 24 hours	90 ml	70 ml
Next 24 hours	70 ml	50 ml

e. Seroma

No cases of seroma were seen with either of the two groups.

f. Systemic Complications

No patient sustained any of the known life threatening complications of dextran-40 like anaphylaxis, congestive cardiac failure, pleural effusion or pneumonia. However, some unique hematological and biochemical abnormalities were noted in the post-operative period in Group (I) (those administered with dextran)

a) Hyperbilirubenemia - One patient had sustained a period of hyperbilirubenemia, for 5 days which remitted on its own on day 7 post op. Max hyperbilirubenemia reached was 4 mg/dl and was direct positive.
b) Post op hemoglobin (Fig 5) - Daily monitoring of the post op hemoglobin was done. The findings were as follows:-

Group I (with dextran)	Group II (without dextran)
5 cases out of 10 had shown a phenomenon of unexplained sudden dip of hemoglobin to 7-8 gm from 10 – 11gms, on 3rd to 4th day without clinical evidence of any obvious blood loss.	Group (II) had no such phenomenon of dip of hemoglobin.

g. Donor site graft loss

Group I (with dextran)	Group II (without dextran)
There were 2 cases of loss of the graft applied over the donor area in this group (one anterolateral thigh flap and another a radial forearm flap). Both cases were managed by dressings and secondary grafting.	Group (II) also had an incidence of donor site skin loss in a case of free fibula donor site. This was also managed with dressings and secondary grafting over the donor site.

DISCUSSION

Thromboses after microvascular tissue transfer have technical and hematologic etiologies. While operative standards have been clinically defined, internationally accepted standards in pharmacologic antithrombotic prophylaxis in reconstructive microsurgery are not clearly outlined yet.

Although flap success rates greater than 95 percent are now routinely achieved [18], microvascular thrombosis is still the prime cause of free-flap failure. Low molecular weight dextran has been used in many older studies as the only mode of thromboprophylaxis in the immediate post op period. But in the recent past, there are studies questioning the very use of anticoagulation in the free flap surgery. Kroll et al. reported 517 consecutive free-tissue transfers without a significant relationship between the use of anticoagulation and thrombosis prevention or flap loss [18].

A study was conducted at our institute to evaluate the Dextran-related complications in microsurgical reconstruction of 20 cases wherein 10 cases in random were administered dextran and the other 10 were not.

Most of the patients with soft tissue defects (65%) in this study were of middle aged (40-50). In the present study, majority of the patients were males (60%). The age of the patient although was not directly associated with flap outcomes, but with increasing age the associated co- morbidities too were observed to me more, and hence the risk of thrombosis and systemic complications had an increased tendency to occur. In their study of 100 consecutive microsurgical reconstructions, Disa et al also found no significant relationship between the age of the patients and the outcome of the flap or the complications from the dextran infusion [19].

The etiologies of the defects were equally post oncological and traumatic in nature in either groups and their distribution in to either group were randomized. The type of the free flaps in either groups of those with dextran and no dextran infusion were similar and were not the confounding factors in this study.

The two groups did not differ significantly with respect to patient age, sex, past medical problems, preoperative radiation, donor or recipient sites, duration of anesthesia (including surgical resection), and duration of hospitalization.

Amongst the 20 cases, the success rates were comparable in either group with only one flap failing in both the groups. Another case of loss of only the skin paddle in an osteocutaneous free fibula flap was observed in Group II (without dextran), but the bone remained viable. Although the sample was very small, the pattern of outcome was comparable in both the groups.

The complications were evaluated as local complications i.e., problems over the flap and the donor site and as the systemic complications. The local complications evaluated included thrombosis, seroma, hematoma, fistula, delayed wound healing, and cellulitis. Two cases (10%) of Group I (with dextran administration) developed subflap hematoma while only one case (5%) in Group II (without dextran administration) developed subflap hematoma and one revealed local suture line infection. Three flaps were re-explored, two for venous thrombosis and one for bleeding (all re-explored flaps were salvaged). There were two cases of partial flap loss and no cases of complete flap loss.

Despite the potential benefits of low-molecular-weight dextran, its use is not without complications. One of the most serious adverse reactions reported is adult respiratory distress syndrome. Kaplan and Sabin reported a case of acute pulmonary edema in a 30-year-old trauma victim after 4 days of infusion of low-molecular-weight dextran. They suggested that a direct toxic effect on pulmonary capillaries as seen with methadone is responsible for the pulmonary complications. Taylor et al. also reported a case of low-molecular-weight dextran–induced, noncardiogenic pulmonary edema in a 30-year-old high-risk patient [14].They suggested a change in the management approach to these patients by eliminating low-molecular-weight dextran.

The two groups did not differ significantly with respect to intraoperative parameters of duration of anesthesia (of comparable microsurgical reconstruction), intraoperative fluids and techniques of reconstruction as same surgical team had operated on all cases.

The complications relating to the dextran were broadly compared as local wound related complications and systemic complications occurring in either group.

The local wound complications included flap loss, pedicle thrombosis, sub flap hematoma, seroma , delayed wound healing and local infection.

One case of partial loss of anterolateral thigh flap was all of loss that was seen with dextran group, whereas one case of complete loss of free fibula and another of loss of skin paddle of the osteocutaneous flap were seen in the group without dextran administration. Kroll et al reported 517 consecutive free-tissue transfers without a significant relationship between the use of anticoagulation and thrombosis prevention or flap loss[18]. Disa et al to reported only one case of partial flap loss in group of 35 who were administered low molecular weight dextran [19]. Pedicle thrombosis was seen in only one case of either groups of that of group I (of dextran administration) wherein on reexploration of the affected anterolateral thigh flap, the pedicle was found thrombosed and with subsequent revascularization the flap was salvaged.

The other local wound complications of hematoma, seroma, and wound infection were comparable in either group in the present study, with two cases of sub flap hematoma in dextran group and only one case in the non-dextran groups. In the above cases, few sutures were removed hematoma drained and the flaps were salvaged. There were no incidences of seroma or local cellulitis or infection in the immediate post-operative period.

Systemic complications of dextran have often been cited as a limiting factor for administration of dextran administration. Many studies like Taylor et al, reported cases of dextran induced acute non cardiogenic pulmonary edema akin to adult respiratory distress syndrome [14]. Dextran induced renal failure has also been reported by Ferraboli et al, and Zwaveling et al [16].

In this study of 20 patients where dextran had been administered for initial 5 days of post-operative period, there were no incidences of any known systemic complications of dextran administration. The complications included: CCF, MI, pulmonary edema, pleural effusion and pneumonia.A transient phenomenon of hyperbilirubenemia lasting for 5 days (direct bilirubin upto 4 mg/dl) was seen in one

patient. This occurred on the 4th post-operative day and remitted on its own. The liver enzymes were seen seen marginally elevated in the 4th post-operative day but returned to normal within a week. The flap was not lost. There were no elevations of renal parameters either in all cases where dextran was administered.

Another interesting phenomenon observed was that of a sudden reduction of blood hemoglobin in the 3rd to 5th day by 3-4 gm% in 5 out of 10 cases where dextran was infused (Fig 5). All these cases were managed by a blood transfusion and the level of hemoglobin were found normalizing after 7th post-operative day. This sudden reduction of hemoglobin was not present in the group which was not administered dextran in the post-operative period. No studies have had similar finding pertaining to dextran when searched for.

In our study, there were near equal donor site graft losses. The dextran group had two cases and the non-dextran group had one case of partial loss of skin graft over the donor site which were initially dressed and later covered by skin graft

There are certain limitations in our study-

1) The sample size is small (n=20).
2) There is no uniformity of the patient demography or type of microvascular reconstructions.
3) There is no histopathological study or microscopic study of the thrombosis.

Conclusion

Low molecular weight dextran has proven to be of no additional benefit in free flap survival according to this study. Although there were no life threatening complications of the dextran in the ten cases who were administered low molecular dextran, there was the interesting findings of unexplained anaemia in the 3rd to 4th post-operative day in majority of these cases. The present study prospectively also demonstrates no significance in addition of low molecular weight dextran in the intraoperative or postoperative scenario of microvascular reconstructions, although there were no systemic complications either.

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