The Rifampicin-bonded Gelseal Graft

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Introduction

Despite the low prevalence rates (0.5–2%)\textsuperscript{1,2}, vascular graft infection can be life-threatening and no effort should be spared to further research that will have direct clinical application.

Many attempts have been made to include antibiotic in graft material in order to provide drug coverage in the immediate perioperative period when the graft is most likely to become infected by direct contamination or blood-borne infection. Richardson \textit{et al.}\textsuperscript{3} attempted simple impregnation of the graft with an antibiotic solution. This gave the thrust to many other research endeavours. The choice of antibiotic has been widely studied, with many authors advocating the effectiveness of rifampicin. Recently Chervu \textit{et al.}\textsuperscript{4} obtained encouraging experimental results using a solution of collagen and rifampicin to impregnate a Dacron graft. Goue-Brissoniere \textit{et al.}\textsuperscript{5} and Avramovic and Fetcher\textsuperscript{6} reported satisfactory prevention of staphylococcal blood-borne and direct contamination using a rifampicin-bonded gelseal graft; this impregnation method relies on the ionic bond that forms between the negatively charged free carboxyl groups in the gelatin and the positively charged molecules of rifampicin.

Recently the Centre for the Study of Vascular Prostheses at the University of Bologna has carried out experimental research into the use of rifampicin-bonded gelseal grafts. An initial study showed that the rifampicin remaining attached to the graft implanted in the blood stream of experimental animals was sufficient to inhabit bacterial growth for up to 72 h after implantation.\textsuperscript{7} A second study demonstrated that the antibiotic-bonded graft was effectively protected from blood-borne infections.\textsuperscript{8}

These data await further confirmation in clinical trials, and the results of two controlled studies are now available.

Materials and Methods

The first prospective study ran from March 1991 to July 1994, and included 600 patients of both sexes and all ages, suffering from chronic peripheral obstructive arteriopathy and/or aortoiliac aneurysm and who received either an aortomono, bifemoral or iliacfemoral vascular graft (Italian Study).\textsuperscript{9} Patients were randomly allocated into two groups: group A received a Vascutek gelseal graft which had been soaked for 15 min in a solution of rifampicin (1 mg/ml of saline) and group B, the control group, receiving an untreated Vascutek gelseal graft. All patients underwent a subcutaneous sensitisation test to ascertain any allergic reaction to rifampicin. All patients received prophylactic antibiotic treatment with cephalosporin (cephalothin, cefazolin, cephamandole) or, if allergic, gentamicin; antibiotic coverage was started 1 h before surgery and continued for 4 days postoperatively. On entry into the study, numerous clinical parameters were assessed for subsequent statistical analysis. Subsequent clinical investigations were carried out at 1, 6, 12 and 24 months. Vascular graft patency, the presence or absence of skin infection, fever or inguinal abscess were noted. When infection was suspected, researchers were asked to follow up with computed tomography (CT)-scan, radio-isotope investigations, blood cultures and any other examination deemed useful for diagnosis of grade 3 graft infection according to the Szilagyi’s classification.\textsuperscript{11}

The second study was performed in several European countries from September 1991 to September 1993, with the aim to evaluate, with the same bonding protocol, the effectiveness in the prevention of early
postoperative wound and graft infection in aorto-
femoral bypass graft (European study). A total of
1276 patients enrolled in group A (rifampicin-bonded
graft) and 1246 in group B (untreated bonded graft).
Subsequent clinical investigation was carried out at 1
month to detect early postoperative wound and graft
infections, according to Szilagyi's classification.

Results

The analysis of epidemiological factors and of the risk
of vascular graft infection in the patient population of
both studies, shows that the groups of patients were
similar in terms of age, sex and predisposing risk
factors.

In the Italian study, during the first year observation
period, 11 cases of infection (1.8%) were observed: five
in group A (1.7%) and six in group B (2.0%). This
difference is not statistically significant. At the second
year of follow-up one more infection was observed in
group B. At this time the total infection rate was 2%
(12/600) and the infection rate in group B was 2.3%
(7/304).

Compared to the uninfected patients, infected
patients showed a significantly higher incidence of
lymphatic complication, and early revision surgery
(p=0.005, p=0.001). Except in two cases, the onset
of infection was always within the first month after
surgery. Staphylococcus aureus was the most frequently
isolated pathogen (50%). In three cases the bacterio-
logical report was not available. Diagnosis of in-
fec tion was mainly clinical and in only four cases were
further investigations (CT-Scan, radioactive isotopes)
carried out. In our view, these examinations would
have been useful to assess the extent of infection,
especially in the early onset cases. Infections had to
fall within grade 3 of Szilagyi's classification.

The European study demonstrated a positive trend
in group A for the prevention of both superficial
wound infection (Grade I: 2.3% vs. 3.5%) and deep
wound infection (Grade II: 0.6% vs. 0.9%). The same
positive trend was observed for graft involvement
(Grade III: 0.3% vs. 0.6%). There was a statistical
difference if Grade I and II wound infections were
combined (2.9% vs. 4.4, p<0.05 vs. control group).

Discussion

The overall infection rate in these clinical studies was
2%, which is in line with the most recent data in
literature. Lymphatic complications and early re-
vision surgery were confirmed as negative prognostic
factors, and inguinal infection proved to be the primary
site of infection.

Experimental data indicate that the antibiotic seems
to remain active on the graft surface for up to 4 days.
Whether this period is sufficient remains in doubt.
Animal studies have shown that the graft retains
bactericidal qualities of antibiotics for the first 2 days.
If the contamination of the graft occurs within this
time then an increased protection should be afforded
against this challenge. If the challenge occurs after this
time it may be that the antibiotic is not present in
sufficient quantity to be bactericidal, but is merely
bacteriostatic. Latent infections can therefore develop
subsequently. Moreover, this short period provides
little or no protection against other pathogenetic mech-
anism s such as late blood borne or lymphatic in-
fec tions.

Some authors have attempted a mix of collagen and
antibiotic which is then sealed on to the graft material,
thereby lodging the antibiotic among the fibres of
the Dacron material. Release of antibiotic into the
surrounding tissue is thus slower, taking place as the
collagen is gradually digested by the host enzymes.
This method has been reported to provide antibiotic
coverage for up to 21 days. In the experimental
observations, antibiotic activity in the bonded graft is
limited to only a few days. However, infections are
known to have very long latency periods and inhibiting
bacterial growth is not synonymous with bacterial
death. Moreover, bacteria are known to increase in
virulence even after months or years in the event of
lowered host immunity.

Conclusions

Both clinical studies showed no statistically significant
benefit from the clinical use of vascular grafts pre-
treated with antibiotic for the prevention of graft in-
fec tion, but the method showed a positive trend. The
only significant data concerned the prevention of early
wound infection. Extending the duration of antibiotic
at the graft site might be desirable. The use of anti-
biotic-bonded gelseal grafts would seem especially
indicated in cases at greater risk for infection, such as
surgical revision cases.

References

1 Cormier JM, Ward AS, Langneau S, Janneau D. Infections
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