JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE 5 (1994) 108–112

The effects of implanted ionomeric and acrylic bone cements on peripheral nerve function

A. R. LOESCHER, P. P. ROBINSON, I. M. BROOK
Department of Oral and Maxillofacial Surgery, University of Sheffield, School of Clinical Dentistry, Claremont Crescent, Sheffield, S10 2TA, UK

The effects of two experimental ionomeric and one commercial acrylic bone cement and set ionomeric microimplant bone substitute (Ionogran®) on peripheral nerve conduction, 1 and 3 weeks after implantation, have been compared. In 44 experiments the rat saphenous nerve was exposed midway between the ankle and thigh and bone cement placed into a pocket created in the connective tissue adjacent to the nerve. In terminal experiments, 1 and 3 weeks later, stimulating electrodes were placed on the saphenous nerve at the ankle, and the amplitude and conduction velocity of the compound action potential (CAP) evoked was recorded through another pair of electrodes positioned on the nerve proximal to the implant, in the thigh. One week after placing an ionomeric bone cement (HVA or V-4), no neural activity could be recorded. Three weeks, after HVA implantation apparently normal CAPs were recorded indicating a recovery from a temporary nerve conduction block, but 3 weeks after V-4 implantation only small CAPs were recorded and these could be attributed to axonal regeneration. After implantation of acrylic bone cement, small CAPs were recorded after 1 week, and within 3 weeks nerve conduction appeared to have completely recovered. Three weeks after placing set ionomeric microimplant particles the amplitude and conduction velocity of the CAP was similar to the controls.

1. Introduction

Previous investigations carried out in this laboratory have shown that when ionomeric (IC) and acrylic bone cements are placed adjacent to a peripheral nerve trunk they cause a block of axonal conduction [1]. In contrast to our findings, clinical observations on patients following placement of ionomeric cement have not revealed any apparent neural disturbance [2, 3]. It is, therefore, possible that bone cements have only a temporary effect on neural function and that spontaneous recovery occurs rapidly. The aim of this study was to determine if and when axonal conduction is re-established after a bone cement is implanted adjacent to a peripheral nerve trunk in an animal model.

The exact manner in which bone cements affect peripheral nerve conduction is not understood. However, it could result from release of methylmethacrylate monomer (acrylic) or polyalkenoic acid/metal ions (ICs) during the polymerization/gelation of the cement or from the exotherm associated with polymerization of acrylic (ICs gell without exotherm).

Conduction block may, thus, be temporary if caused by an imbalance of ions within the tissue fluid surrounding the nerve trunk, or more permanent if the chemical/thermal insult is severe enough to cause axonal degeneration. In the latter case, neural function can only be restored if axons regenerate from the site of injury to their peripheral receptors. To establish whether any recovery in neural activity was the result of a reversal of a temporary nerve block or was due to axonal regeneration, control experiments where the nerve was frozen were undertaken. Freezing causes degeneration of all the axons distal to the injury site, and any neural activity recorded after such an injury must be the result of axonal regeneration. Recovery from a temporary nerve block may be rapid (minutes or hours), but regenerating axons may take weeks to reach their peripheral receptors (depending upon the regeneration distance). Comparison of the time-course of recovery with that of the controls should, therefore, distinguish between the different causes of nerve conduction block.

2. Methods

2.1. Surgery

Adult male wistar rats, 4–5 months in age and weighing 200–300 g, were anaesthetized using halothane (May and Baker Ltd, UK; induction 4% in oxygen, maintenance 1.5% in oxygen). Body temperature was maintained at $37.5 \pm 0.2\,^{\circ}C$ by an electric blanket thermostatically controlled from a rectal thermistor. Under aseptic conditions the saphenous nerve was exposed midway between the ankle and the point where it branches from the main femoral trunk in the thigh. A pocket measuring approximately 0.5 cm by 0.3 cm was then created within the connective tissue overlying the nerve, taking care to leave the epineurium intact. Bone cements were placed into the

0957–4530 ©1994 Chapman & Hall

pocket and the connective tissue opening was closed with a 9/0 monofilament polyamide suture (Ethicon, UK). No attempt was made to displace the nerve from the adjacent blood vessels or elevate it from the underlying muscle.

A total of 44 saphenous nerves were prepared in this way and the experiments divided into six groups as follows:

1. Eight had V-4 ionomeric cement (Ionos GmbH and Co, Seefeld, Germany) placed in the pocket and were allowed to recover for either 1 week (four experiments) or 3 weeks (four experiments).
2. Eight had HVA ionomeric cement (Ionos, Germany) placed in the pocket and were allowed to recover for either 1 week, (four experiments) or 3 weeks (four experiments).
3. Eight had acrylic bone cement (Surgical simplex, Howmedica, Kiel, Germany) placed in the pocket and were allowed to recover for either 1 week (four experiments) or 3 weeks (four experiments).
4. Four had set ionomeric porous microimplant particles. (Ionogran®, Ionos, Germany) placed in the pocket and were allowed to recover for 3 weeks. As previous work [1] reported that set ionomeric micoimplant particles had no immediate effect on peripheral nerve function, the 1 week recovery period was omitted.
5. Eight were controls without implants. A pocket was created and sutured and the animals allowed to recover for either 1 week (4 experiments) or 3 weeks (four experiments).
6. Eight were regeneration controls. At the site of the pocket the saphenous nerve was frozen with three consecutive applications of liquid nitrogen on pledgets of cotton wool and the animals allowed to recover for either 2 weeks (four experiments) or 3 weeks (four experiments).

The bone cements were mixed according to the manufacturer's instructions (see Table I). The ICs came in prepacked capsules and were mixed in a machine (Ionomix®, Ionos). The acrylic was mixed for 30 s using a plastic container and spatula. Table I shows the mixing and placement times of the cements. All animals received 0.1 ml/kg oxytetracycline i.m. (Terramycin, Pfizer Ltd, UK).

At the end of the recovery periods a terminal experiment was carried out under anaesthesia (induction: halothane 4% in oxygen and 0.5–0.8 ml of a mixture of ketamine, 66.6 mg/ml, and xylazine, 6.6 mg/ml, intraperitoneal; maintenance 0.2 ml ketamine, 100 mg/ml, IV as required, Bayer, UK and Park Davis and Company, UK). The heart rate was monitored throughout the experiment and body temperature maintained at 37.5 ± 0.2 °C. The saphenous nerve was exposed central to the site of the previous surgery, at a point near to where it branches from the main femoral trunk. The proximal end of the nerve was sectioned and the loose connective tissue surrounding it gently removed over a distance of 1–1.5 cm so that the nerve could be elevated from the underlying muscle. A pool was created around the nerve and filled with warmed liquid paraffin, and the sectioned end of the nerve was placed on a pair of platinum wire recording electrodes (0.15 mm diameter). Near to the ankle a branch of the saphenous nerve was isolated from the surrounding tissues over a distance of 3–4 mm by inserting a small piece of parafilm (American National Can, UK) beneath the nerve. A second pool filled with warmed liquid paraffin was created, and a pair of platinum wire electrodes (0.15 mm diameter) was positioned across the nerve. A series of electrical stimuli (10 V and 0.1 ms duration) was applied to these electrodes at 1 s intervals while recording the averaged response proximally. Data were analysed using an IBM computer, SP12 interface and software (Grafitek, UK). The peak-to-peak amplitude of the compound action potentials and the conduction velocity of the fastest components were recorded. Statistical analysis was carried out using Student's t-test where appropriate.

TABLE I Mixing, setting and placement times of acrylic and ionomeric bone cements (IC). Setting times for the ICs were measured using a rheometer

Material	Mixing time (s)	Placement time (s)	Setting time (min:s)
Acrylic	30	120	17:30
V-4 IC	35	10	4:30
HVA-IC	55	10	6:30

3. Results

3.1. Controls without implants

Two weeks after a nerve freeze injury no CAPs were recorded (Fig. 1) but after 3 weeks small CAPs were visible with a mean amplitude of 0.10 ± 0.11 (SD)mV and mean conduction velocity of $11.6 \pm 2.7\ m\,s^{-1}$.

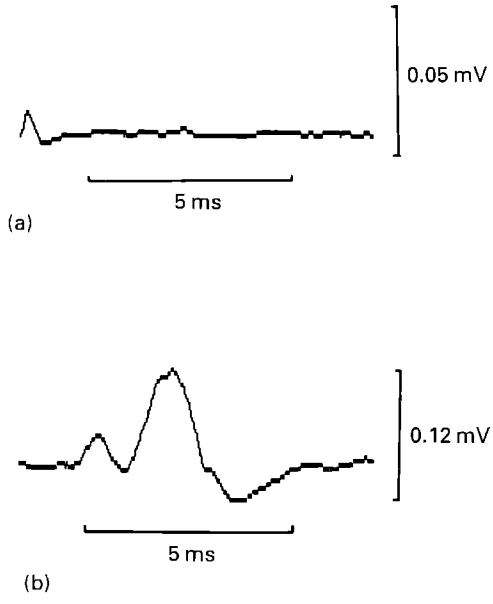

Figure 1 Responses recorded from the saphenous nerve during electrical stimulation (10 V, 0.1 ms) distal to the injury site. Each sequence is the average of 10 consecutive recordings made at 1 s intervals: (a) 2 weeks; and (b) 3 weeks after a nerve freeze injury.

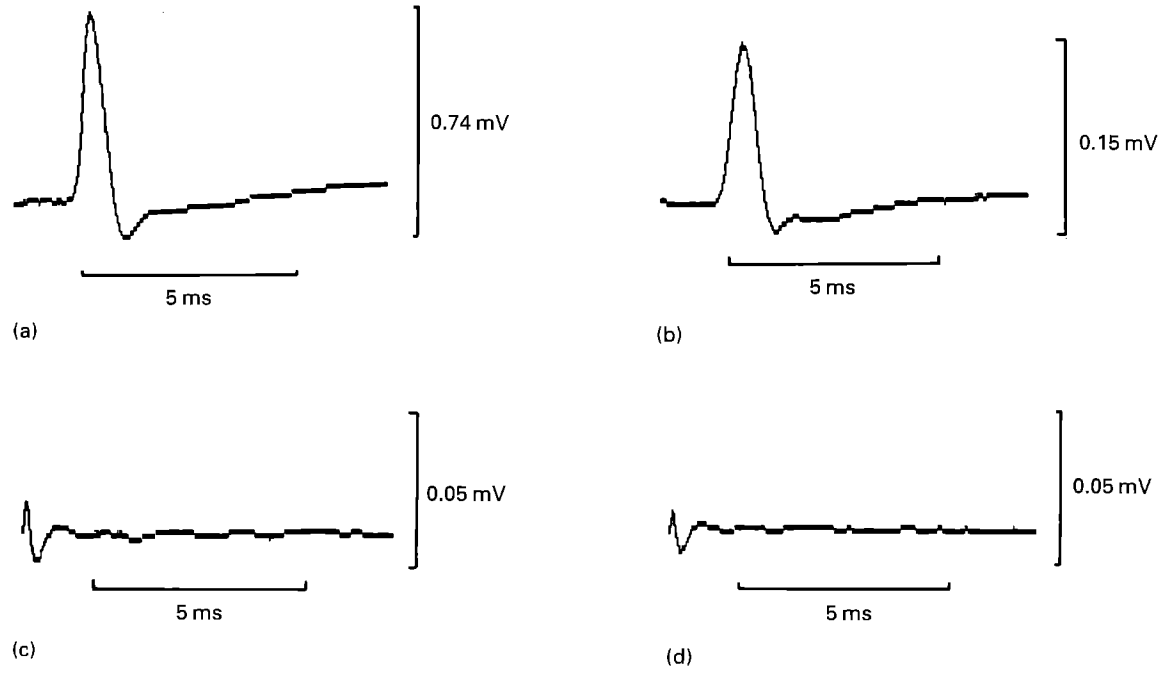

Figure 2 Responses recorded from the saphenous nerve during electrical stimulation (10 V and 0.1 ms duration) distal to the injury site after a 1-week recovery period. Each sequence is the average of 10 consecutive recordings made at 1 s intervals: (a) controls; (b) acrylic bone cement; (c) HVA ionomeric cement; (d) V-4 ionomeric cement.

The mean amplitude was, however, significantly smaller than in the control animals without implants as was the conduction velocity, non-implanted controls having an amplitude of 1.4 ± 0.8 mV ($p < 0.005$) and conduction velocity of 37.5 ± 5.3 ms^{-1} ($p < 0.001$).

3.2. One-week recovery

One week after placing IC (HVA or V-4) adjacent to the nerve trunk no CAPs could be recorded (Fig. 2 and Tables II and III). In three of the four experiments in which acrylic cement was positioned adjacent to the nerve, the averaged CAPs recorded had a mean peak-to-peak amplitude of 0.31 ± 0.39 mV which was significantly smaller than the controls (0.91 ± 0.19 mV, $p < 0.05$) but the mean conduction velocity (24.7 ± 4.8 $m\,s^{-1}$) of the CAPs was not significantly different from the controls 33.5 ± 4.6 $m\,s^{-1}$, $p > 0.5$). In the remaining acrylic experiment no CAP was recorded.

TABLE II The mean peak-to-peak amplitude and standard deviation (mV) of the averaged compound action potentials recorded for each of the experimental groups

	Recovery period 1 week	Recovery period 3 weeks
Controls (none implanted)	0.91 ± 0.19	1.40 ± 0.84
Freeze controls	–	0.1 ± 0.11
Acrylic	0.31 ± 0.39[a]	0.64 ± 0.29
HVA-IC	No CAP recorded	0.60 ± 0.62
V-4-IC	No CAP recorded	0.06 ± 0.04
Set ionomeric particles Ionogran®	–	2.23 ± 1.45

[a] Only three of four experiments included in this analysis, as in one experiment no neural activity was recorded.

TABLE III The mean conduction velocity and standard deviation ($m\,s^{-1}$) of the averaged compound action potentials recorded for each of the experimental groups

	Recovery period 1 week	Recovery period 3 weeks
Controls (none implanted)	33.5 ± 4.6	37.5 ± 5.3
Freeze controls	–	11.6 ± 2.7
Acrylic	24.7 ± 4.8[a]	35.9 ± 5.6
HVA-IC	0	33.5 ± 15.4
V-4-IC	0	17.2 ± 6.8
Set ionomeric particles Ionogran®	–	40.7 ± 3.1

[a] Only three of four experiments included in this analysis, as in one experiment no neural activity recorded.

3.3. Three-week recovery

Some recovery of nerve conduction had occurred in all the experiments 3 weeks after placing the bone cements (Fig. 3). The mean conduction velocity and peak-to-peak amplitude of the CAPs recorded after placing set ionomeric porous microimplant particles, acrylic cement and HVA ionomeric bone cements were not significantly different from the controls in which no material was implanted (Tables II and III).

Three weeks after placing V-4 IC the mean conduction velocity (17.2 ± 6.8 $m\,s^{-1}$) and peak-to-peak amplitude (0.06 ± 0.04 mV) of the CAP recorded were both significantly reduced compared with the non-implanted controls (conduction velocity 37.5 ± 5.3 $m\,s^{-1}$, $p < 0.02$; amplitude 1.40 ± 0.84 mV, $p < 0.05$).

The mean amplitude and conduction velocity of CAPs recorded 3 weeks after a nerve freeze (amplitude 0.1 ± 0.11 mV; conduction velocity 11.6 ± 2.7 $m\,s^{-1}$) were significantly different from those

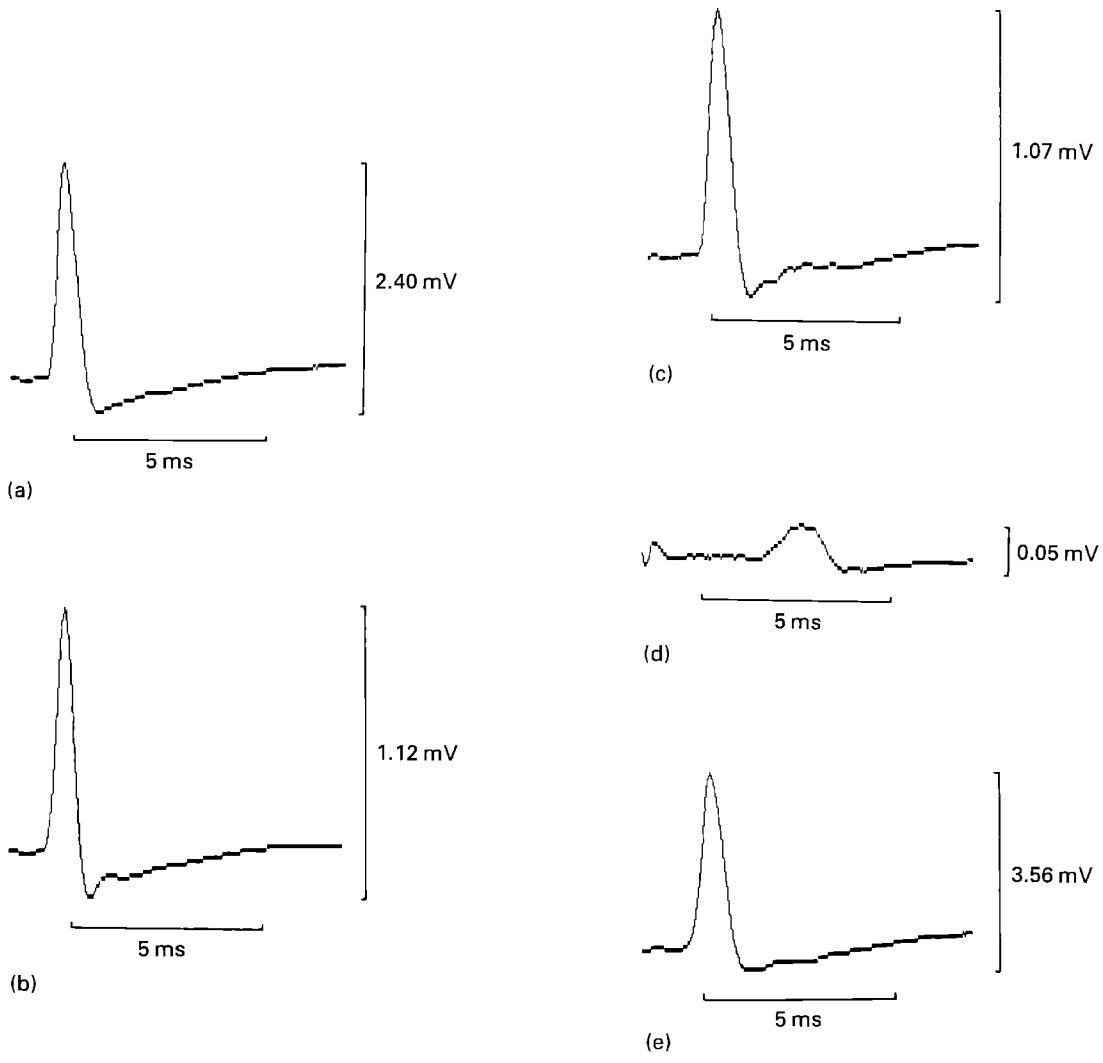

Figure. 3 Responses recorded from the saphenous nerve during electrical stimulation (10 V and 0.1 ms duration) applied distal to the site of injury after a 3-week recovery period. Each sequence is the average of 10 consecutive recordings made at 1 s intervals: (a) controls; (b) acrylic bone cement; (c) HVA ionomeric cement; (d) V-4 ionomeric cement; (e) set ionomeric microimplant particles.

recorded 3 weeks after placing acrylic (amplitude 0.64 ± 0.29 mV, $p < 0.05$; conduction velocity $35.9 \pm 5.6\ m\,s^{-1}$, $p < 0.001$) and set ionomeric porous microimplant particles (amplitude 2.23 ± 1.45 mV $p < 0.05$; conduction velocity $40.7 \pm 3.1\ m\ s^{-1}$, $p < 0.001$). However, the mean amplitude and conduction velocity of the CAPs recorded 3 weeks after a nerve freeze injury were not significantly different from those recorded 3 weeks after placing V-4 ionomeric cement (amplitude 0.06 ± 0.04 mV, $p > 0.5$, conduction velocity $17.2 \pm 6.8\ m\,s^{-1}$, $p > 0.05$). Although the amplitude of the CAPs recorded after nerve freeze was not significantly different to that recorded 3 weeks after placing HVA ionomeric cements (0.60 ± 0.62 mV), the mean conduction velocity was significantly slower (HVA, $33.5 \pm 15.4\ m\,s^{-1}$, $p < 0.05$).

4. Discussion

Electrical stimulation of a peripheral nerve evokes a compound action potential (CAP), the area beneath which reflects the sum of activity in all the individual axons. The absolute size of any CAP depends on many factors associated with the recording conditions, such as the amount of connective tissue around the nerve and the interelectrode distance. In this study, as each action potential was recorded under slightly different conditions, direct comparisons between the size of the CAPs must be made with caution.

Freezing a peripheral nerve causes minimal disruption of the perineurium, epineurium and endoneurium, and regeneration is rapid and relatively complete [4, 5]. Two weeks after freezing the saphenous nerve no CAPs could be recorded showing that the injury had affected all of the axons and also that no axons had regenerated as far as the site of the distal electrodes at that stage. By 3 weeks, however, some regenerating axons had reached the site of the distal electrodes, giving small CAPs with slow conduction velocities. Early regenerating axons have small diameters and their conduction velocities are correspondingly slow [6]. This control data permits us to conclude that any responses recorded 1 week after the application of bone cements must be attributed to recovery from temporary conduction block and not to regeneration of damaged axons. Responses recorded after 3 weeks which are comparable to those recorded after nerve freeze, could be attributed to regenerating axons.

One week after placing both HVA and V-4 ionomeric bone cements adjacent to the saphenous nerve no CAPs could be recorded. Three weeks after implanting HVA cement the mean conduction velocity and amplitude of the CAPs recorded were similar to those of the controls, suggesting that there had been recovery from temporary conduction block. In contrast, 3 weeks after implanting V-4 ionomeric cement the CAPs were comparable to those recorded after nerve freeze injury, suggesting that this recovery was due to axonal regeneration. The formulation of the two ionomeric cements may explain these differences. It was also noted that HVA IC 'dissolved' in the tissues and there was thus little material left at 3 weeks. The loss of HVAIC was probably due to contamination of the unset cement by tissue fluid; in clinical use ICs are placed in a dry field on bone.

In a previous study we demonstrated that neural conduction is blocked within two minutes of placing acrylic cement adjacent to a peripheral nerve [1]. We have also confirmed that if the acrylic is applied in the same way as described in the present experiments, rapid block of nerve conduction occurs. In the present experiments compound action potentials with small amplitudes were recorded 1 week after implanting the acrylic and must, therefore, have resulted from a reversal of a temporary nerve block. After a 3-week recovery period the amplitude and the conduction velocity of the CAPs recorded were similar to the controls indicating that the recovery was complete. It has been suggested that the heat produced from the exothermic setting reaction of the acrylic might cause axonal degeneration but this clearly did not occur in the present study. However, the quantity of acrylic used was small and a greater mass may have caused a more severe injury.

We previously reported that partially set IC had no effect on nerve conduction for over 10 min, whereas acrylic caused conduction block within 2 min [1]. Together with the results from the present specially designed animal experiments, this suggests that if polyalkenoate acid is released from ionomeric cements during gelation it is slow to diffuse through the connective tissues compared with methylmethacrylate monomer. However once it has reached the nerve it produces a more severe nerve injury.

Porous microimplant particles (Ionogran^{R}) had no effect on neurone conduction either immediately after it was placed adjacent to a peripheral nerve [1] or after it had been implanted in the tissues for 3 weeks.

Overall our data suggest that caution should be taken when placing any bone cement adjacent to a peripheral nerve.

Acknowledgements

The authors thank Mrs S Bodell and Mrs A Long for their excellent technical support. This work was supported by Ionos, Medizinische Produkte GmBH & Co KG, D–82229 Seefeld, Germany.

References

1. A. R. LOESCHER, P. P. ROBINSON and I. M. BROOK, Submitted to *J. Mater. Sci.* (in press).
2. R. T. RAMSDEN, R. C. D. HERDMAN and R. H. LYE, *J. Laryngology Otology* **160** (1992) 949.
3. G. BABIGHIAN *ibid.* **160** (1992) 954.
4. D. C. CARTER, W. R. LEE, W. GILL and R. J. JOHNSTON, *R. Coll. Surg. Edinb.* **17** (1972) 25.
5. A. R. LOESCHER and P. P. ROBINSON, *Brain Res.* **536** (1990) 257.
6. L. GUTH, *Physiol. Rev.* **36** (1956) 441.

Received 26 July
and accepted 14 September 1993