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

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A total of 44 rat saphenous nerves were isolated. A pair of stimulating electrodes was positioned distally (at the ankle) to evoke a compound action potential (CAP) which was recorded proximally (in the thigh) through another pair of electrodes. Bone cement was then placed adjacent to the nerve midway between the electrodes and changes in the CAP recorded over a 30-min period. Nerve conduction was completely blocked within 2 min of placing unset acrylic bone cement adjacent to the nerve. The experimental ionomeric cements (IC) also caused a reduction in the nerve conduction although this did not usually occur until the cement had been positioned adjacent to the nerve for over 10 min. Slow-setting IC blocked nerve conduction more quickly than fast-setting IC but there was no apparant difference between the effects of applying materials early or late in the setting reaction. Set ionomeric porous microimplant particles (Ionogran®) had no effect on neural function.

1. Introduction

Acrylic and glass ionomer bone cements are both introduced into the body during reconstructive surgical procedures [1–3]. Bone cements based on acrylic are widely used and improved formulations are being developed [4] but they still suffer from two major disadvantages. Firstly, during setting a marked exothermic reaction occurs that may result in thermal damage to the surrounding tissues [5] and second, the release of methyl methacrylate monomer into the tissues may cause chemical necrosis [6]. A novel group of ionomeric cements (ICs) based on a neutralization reaction between aluminosilicate glass and organic polyalkenoic acid are being developed for use as bone cements [1, 3, 7]. Preliminary trials using ICs for the reconstruction of the middle ear [1, 3, 8] and for the repair of craniofacial defects [9] have suggested that these cements have few side effects. However, although these cements are used in situations where they come into close contact with peripheral nerves (i.e. in the middle ear and in the mandible during jaw augmentation) there have been no previous investigations to determine their effect on peripheral nerve function, and this was the aim of the present study.

Electrical stimulation of a peripheral nerve evokes a compound action potential (CAP), the area beneath which reflects the sum of the activity in all the individual axons in the nerve trunk. Changes in the area of a CAP (provided the recording conditions remain constant) therefore reflect changes in either the number of axons conducting impulses or in the size of the individual action potentials. In these experiments an evoked CAP was recorded and then, without changing the experimental arrangement, repeated recordings of the CAP were made after either the IC or acrylic bone cement had been placed adjacent to the nerve. Any reduction in the size of the CAP could then be attributed to either a reduction in the number of axons conducting action potentials or to a reduction in the size of individual action potentials.

The effect of a cement on nerve conduction may be influenced both by its setting time and by the period, after mixing is complete, before it is positioned adjacent to the nerve (placement time). For this reason it was decided to evaluate set ionomeric porous microimplant particles of IC and freshly mixed IC formulated with different setting times (slow, medium and fast). The effect of different placement times (either immediately after mixing was completed or just prior to setting) were also investigated.

2. Method

Adult male wistar rats, 4–5 months of age and weighing 200–300 g were anaesthetized using a 2:1 ketamine/xylazine mix (Bayer, UK and Park Davis, UK; Induction, 2ml/kg i.p. and maintenance 0.2 ml of ketamine s.c. as required). The trachea was cannulated and the heart rate monitored throughout the experiment. Body temperature was maintained at 37.5 $\pm$ 0.2 °C by an electric blanket thermostatically controlled from a rectal thermistor. The saphenous nerve in the rats hind limb was exposed from the point where it branches from the main femoral trunk in the thigh, to the ankle where it divides into multiple branches.

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 it could be elevated from the underlying muscle. The connective tissue overlying the remainder of the nerve was then gently teased away but in all cases care was taken to

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ensure that the epineurium and perineurium remained intact and no attempt was made to either separate the nerve from the adjacent blood vessels or elevate it from the underlying muscle. 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, USA) beneath the nerve. Three separate pools were then created around the saphenous nerve by flowing liquid agar (temperature 42 °C) over the nerve preparation (Fig. 1). The agar was then gently removed in the area of the three pools once it had solidified (Fig. 1). On each occasion the middle pool was 1 cm long and 0.5 cm wide and was initially filled with Ringers solution. The proximal and distal pools were filled with warmed liquid paraffin. In the proximal pool the sectioned central portion of the saphenous nerve was placed on a pair of platinum wire recording electrodes (0.15 mm diameter). A second pair of platinum wire electrodes (0.15 mm diameter) was positioned across the nerve in the distal pool and electrical stimuli applied to these electrodes while recording proximally. Responses were recorded to a series of 10 stimuli of 10 V and 0.1 ms duration and 30 stimuli of 30 V and 1 ms duration, each of which were applied to the nerve at 1-s intervals. Responses were averaged and stored at 2, 5, 15 and 30 min in the controls, and at 2, 5, 10, 15, 20, 25 and 30 min after placing the cement material adjacent to the nerve, using an IBM computer, SPI2 interface and software (Grafitek, UK). Care was taken not to disturb the experimental arrangement between recordings.

A total of 44 saphenous nerves were prepared and CAPs recorded as described above. The experiments can be divided into six groups (Summarized in Table I).

1. Four served as controls with Ringers solution placed in the middle pool.
2. Four had set iononomeric porous microimplant particles. Ionogran®; Ionos GmbH and Co KG, D-82229, Seefeld, Germany), moistened with Ringers solution, placed in the middle pool.
3. Eight had slow set IC (V-1, Ionos, Germany) placed in the middle pool either 1 min (four experiments), or 6 min and 30 s (four experiments), after mixing was complete.
4. Eight had medium set IC (V-2; Ionos, Germany) placed in the middle pool either 1 min (four experiments), or 3 min and 30 s (four experiments), after mixing was completed.

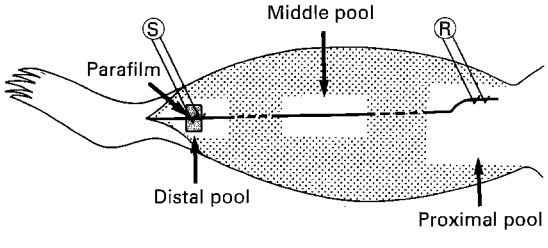

Figure 1 The experimental arrangement showing the position of the three pools. The pools were created by flowing liquid agar over the tissue and then, once it had solidified, by gently removing it from around the nerve.

TABLE I Setting times and placement times for IC and acrylic bone cements. All IC cements were mixed for 20 s. Acrylic was mixed for 30 s

Material	Setting time min/s	Time (Min/s) Material placed on nerve		
	–	1ST	2ND	3RD
Isomeric particles		0	–	–
Fast Setting V-3	3/00– 3/40	1	2/30	–
Medium Setting V-2	4/30– 5/00	1	3/30	–
Slow Setting V-1	7/15–11/30	1	6/30	–
Acrylic	15/00–20/00	1	5/00	15/00

5. Eight had fast set IC (V-3; Ionos, Germany) placed in the middle pool either 1 min (four experiments), or 2 min and 30 s (four experiments), after mixing was completed.
6. Twelve had acrylic bone cement (Surgical Simplex; Howmedica, Kiel, Germany) placed in the middle pool either 1 min (four experiments), 5 min (four experiments), or 15 min (four experiments) after mixing was completed.

All the materials tested above were prepared as the manufacturers directed. The ICs came in prepacked capsules which were mixed for 20 s using a mixing machine (Ionomix®, Ionos GmbH & Co, Germany). The acrylic was mixed for 30 s using a plastic container and spatula.

After completion of the experiment a hard copy of the averaged CAPs was obtained and the area under the rectified action potential was measured using a digitizing pad, IBM computer and software (Bioquant, R&M Biometrics, Nashville, TN, USA). The area beneath each CAP was then expressed as a percentage of the area of the initial (prematerial) CAP (i.e. the CAP recorded before the test material was placed in the middle pool).

3. Results

Except for the set granular ionomeric microimplant material, all the materials in this study had some inhibitory effect on nerve conduction. Figs 2–12 show the changes in the areas under the rectified compound action potentials when a series of 10 V stimuli were applied for each animal. The changes in the areas under the CAP recorded when a series of 30 V stimuli applied were similar and are not illustrated separately. Figs 2–10 show changes in the area of the compound action potential as expressed as a percentage of the area of the initial (prematerial) CAP.

3.1 Controls

In the control experiments (Fig. 2) there were some change in the area under the CAPs over the 30-min recording period. In one experiment the area of the CAP increased by 36% and in another it decreased by 17%. Similar variations in the area under the CAP was also seen after placing the set ionomeric porous microimplant particles (Fig. 3). However, in none of these experiments did the set ionomeric porous microimplant particles cause the area under the CAPs to fall

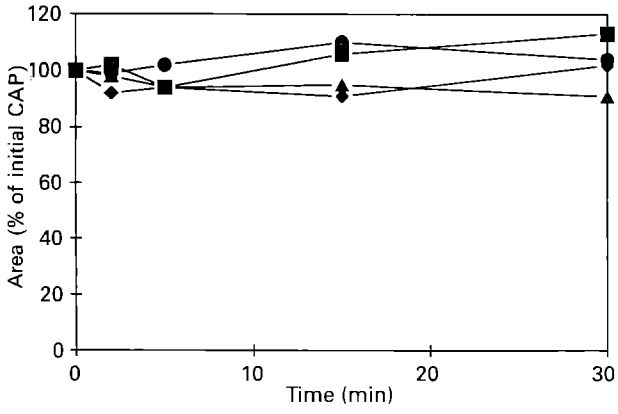

Figure 2 Control experiment; Ringers solution placed in the middle pool.

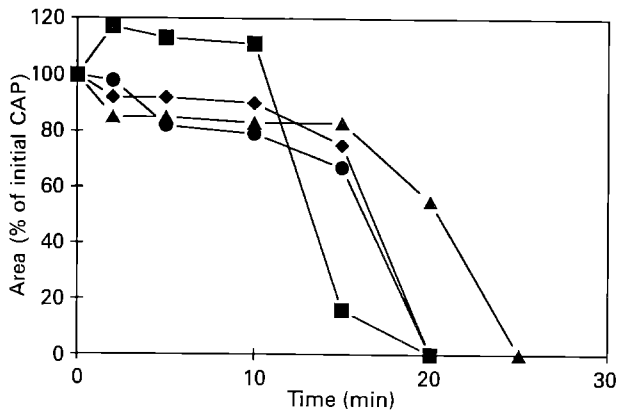

Figure 4 Slow-set IC (V-1) placed in the middle pool 1 min after mixing was complete.

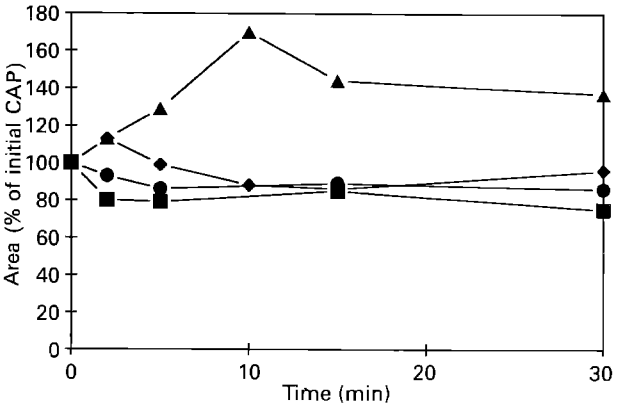

Figure 3 Set ionomeric porous microimplant particles placed in the middle pool.

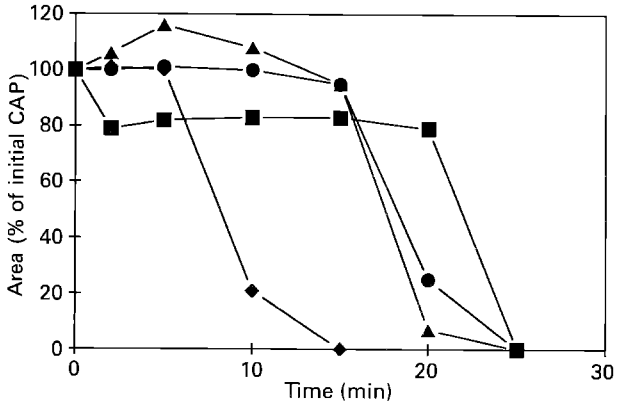

Figure 5 Slow-set IC (V-1) placed in the middle pool 6 min and 30 s after mixing was complete.

by more than 25% of the area recorded under the initial (prematerial) CAP.

3.2. Ionomeric cements

The slow-setting IC (V-1) (Figs 4 and 5) and the medium set IC (V-2) (Figs 6 and 7) both had a marked inhibitory effect on saphenous nerve conduction; within a 30-min period the nerve had ceased to conduct impulses and no CAPs could be recorded. Fig. 10 shows the changes in a CAP which was recorded when a slow-setting IC was placed in the middle pool.

The fast-setting IC (V-3) had a more variable effect on the neural tissues (Figs 8 and 9). In two experiments the fast-setting IC caused no decrease in the size of the CAPs during the 30-min recording period. Nerve conduction was therefore studied for a further 30 min but no substantial changes in the CAPs were noted. However, in the remaining six experiments the size of the CAP recorded after the material had been positioned adjacent to the nerve for a 30-min period was significantly reduced (Figs 8 and 9).

The time duration between the completion of mixing and the placement of an ionomeric cement did not appear to alter the effect of each cement on neural function (compare Fig. 4 with Fig. 5; Fig. 6 with Fig. 7; Fig. 8 with Fig. 9).

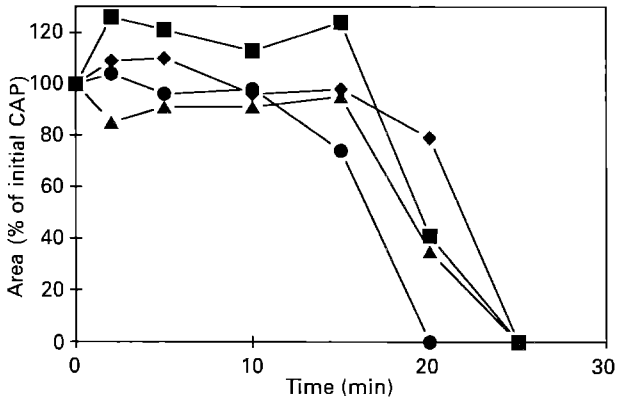

Figure 6 Medium-set IC (V-2) placed in the middle pool 1 min after mixing was complete.

3.3 Acrylic cement

The acrylic cement applied either 1 or 5 min after mixing caused a rapid block of nerve conduction and no CAPs were recorded after 2 min. Fig. 12 shows the rapid decay (within 1 minute) of the CAP after placing acrylic cement (dough stage) in the middle pool. This figure shows that during the first 20 s after placing the cement adjacent to the nerve no change in size or latency of the CAP occurred, this was followed by an increase in the latency (indicating a decrease in rate of

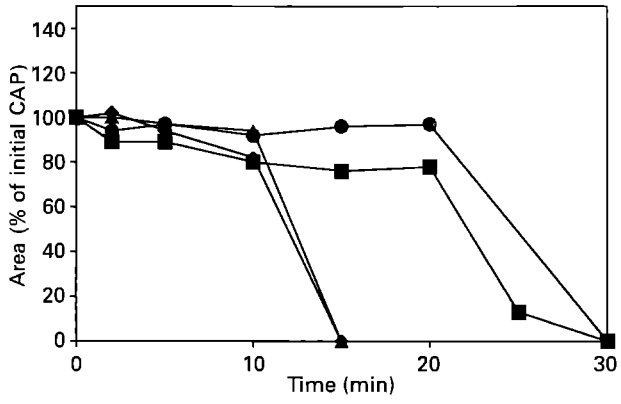

Figure 7 Medium-set IC (V-2) placed in the middle pool 3 min and 30 s after mixing was complete.

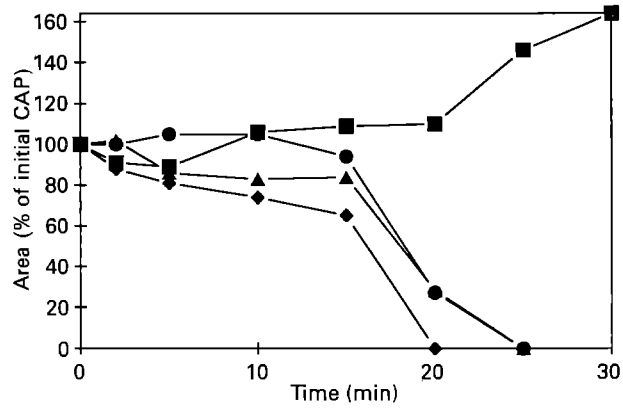

Figure 8 Fast-set IC (V-2) placed in the middle pool 1 min after mixing was complete.

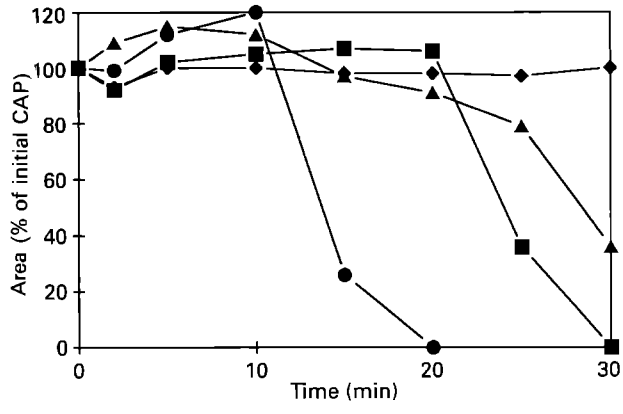

Figure 9 Fast-set IC (V-3) placed in the middle pool 2 min and 30 s after mixing was complete.

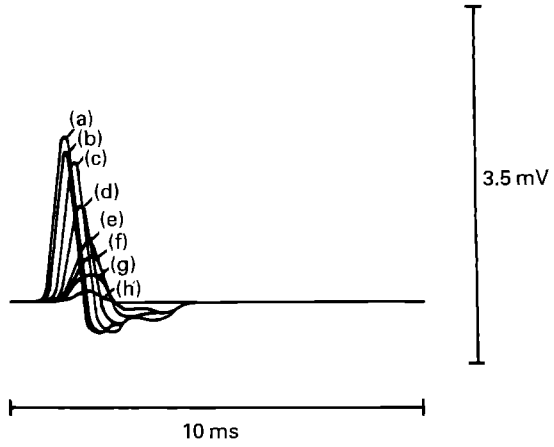

Figure 10 The averaged compound action potentials recorded when 10 V, 0.1 ms duration stimuli were applied after placing slow-setting ionomeric cement (V-1) adjacent to the nerve: recorded after (a) 2 min; (b) 5 min; (c) 10 min; (d) 12 min; (e) 14 min; (f) 16 min; (g) 18 min; (h) 20 min.

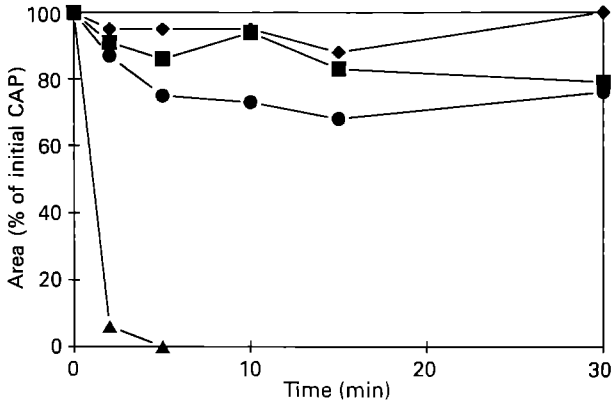

Figure 11 Acrylic bone cement placed in the middle pool 15 min after mixing was complete.

3.4. Compound action potential

Electrical stimulation using a 10 V stimulus evokes a CAP which results largely from activity in Aβ fibres and the mean conduction velocity of the fastest components in the response was $42.2 \pm 4.8\ m\,s^{-1}$ in the control animals (Fig. 13). When a 30 V stimulus was applied the CAP was found to consist of two peaks — the Aβ and Aδ fibres. The mean condition velocity of the Aδ component was $10.2 \pm 1.8\ m\,s^{-1}$ (Fig. 14). No C fibre responses were seen in the CAPs recorded during these experiments.

4. Discussion and conclusions

Both IC and acrylic bone cements caused a block of nerve conduction in the animal model used in this study. The manner in which the ICs act on the neural tissue to block conduction is not clear although the release of organic acid or metal ions from the unset cement may be responsible. Other studies have shown that as gelation of IC progresses the amount of free polyalkeonate acid reduces [10, 11]. However, in these experiments it was noted that the nerve block occurred after the ionomeric cement had set. This

conduction), a rapid reduction in size of the CAP, and within 50 s only a small CAP could be recorded. The block of nerve conduction after placing liquid cement was equally rapid. By contrast, acrylic placed when it was nearly set, at the late dough stage (15 min after mixing), (Fig. 11) had little effect on the CAP in three experiments, but in one experiment the size of the CAP rapidly decreased and within 5 min no CAP was visible.

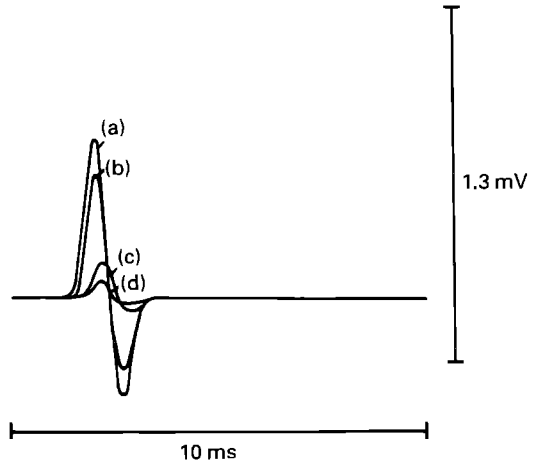

Figure 12 The averaged compound action potentials recorded before and within 60 s of placing acrylic bone cement at the dough stage of set (i.e. 5 min after mixing was complete) adjacent to the nerve. Each CAP is the response to a 10 V stimuli of 0.1 ms duration: (a) before the placement of the acrylic and after 20 s; (b) 30 s; (c) 40 s; (d) 50 s.

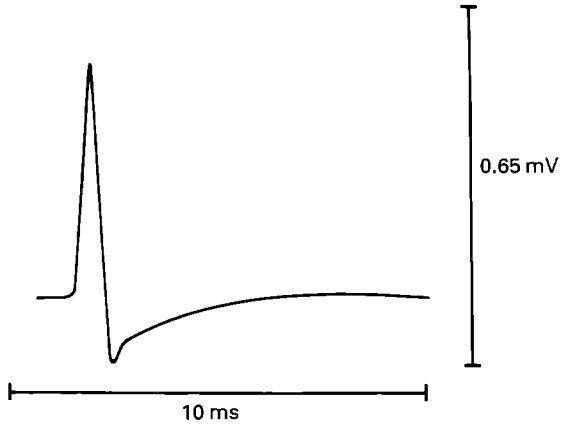

Figure 13 The averaged compound action potential recorded when a series of 10 stimuli, of 10 V and 0.1 ms duration, were applied to the nerve at 1 s intervals in a control experiment.

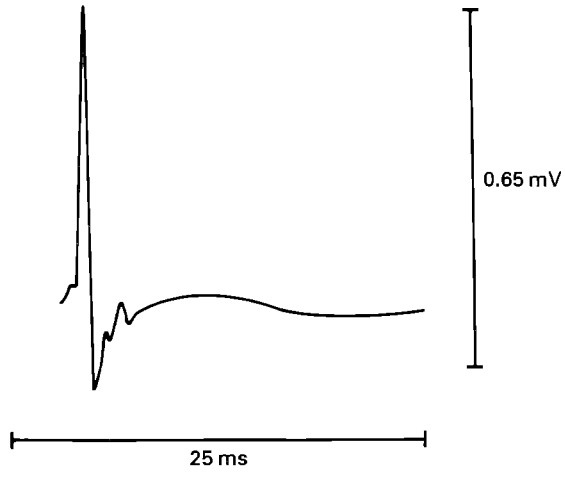

Figure 14 The averaged compound action potential recorded when 30 stimuli of 30 V and 1 ms duration were applied to the nerve at 1 s intervals in a control experiment.

presumably reflects the time taken for ions to diffuse across the connective tissue sheaths surrounding the nerve. It might be expected that materials placed soon after mixing (i.e. 1 min after mixing was complete; Figs 4, 6, 8) would release greater amounts of polyalkenoate acid or metal ions and therefore have a more severe effect on neural function than those placed just prior to their setting point (Figs 5, 7, 9). The present study, however, failed to show any differences between the materials applied early and late in the setting reaction.

The duration of the setting reaction (setting time) also influences the period during which the nerve is exposed to elutants from the setting cement; materials with a fast set have a shorter period during which components are free to diffuse into the tissues before they become bound into the polymer structure. Although in this study all the ICs under test exhibited a potential for blocking nerve conduction, the slower-setting cements (V-1 and V-2) inhibited the neural function more rapidly than the faster-setting cement (V-3). Figs 8 and 9 show that the fast-setting IC was positioned adjacent to the nerve for 20 min before any reduction in the size of the CAP occurred and in one experiment this cement was found to have no effect on nerve conduction. Among the clinical advantages of the IC are their "snap set" and the ability to control their setting and mixing times by careful formulation. The development of cements with both a predictable and quick snap set, timed to occur just after placement, will enable a reduction in the *in vivo* gelation time and should, therefore, reduce their effects on neural function. Set ionomeric porous microimplant particles had no significant effect on nerve conduction during the periods studied.

Acrylic cement may damage the neural tissues in two ways. First, by the release of monomer and, secondly, due to the exothermic setting reaction. Nerve conduction block seems most likely to be due to the release of monomer during polymerization as it occurs early in the setting reaction (during the time when acrylic is used clinically), the main exothermic reaction occurring 15 min after mixing is complete. This hypothesis is also supported by the observation that it was possible to induce some recovery of the CAP by removal of the acrylic and irrigation of the tissues (this was also observed with IC). During the exothermic reaction, however, the temperature of the acrylic cement rises to over 80 °C (unpublished observations) and this may result in severe nerve damage secondary to the nerve block which results from monomer release. In one experiment 10 min after placing nearly set acrylic (15 min after mixing was completed) adjacent to the nerve no CAP was recorded (Fig. 10): this was in contrast to the other three experiments in this group in which the set acrylic appeared to have no effect on the nerve conduction. There are two possible explanations for this variable response. First, although in all experiments an effort was made to preserve a substantial and similar amount of connective tissue around the nerve (similar to that which would be retained in a clinical situation), there may have been some differences. Secondly, the variability may reflect the variation in the time of onset of the exothermic reaction under slightly different temperature conditions and handling of the material.

In the control experiments some small variations in the size of the CAP were found during the 30-min recording period. This is an inevitable effect of slight changes in the recording conditions such as the accumulation of tissue fluid around the electrodes. However, in those materials which affected neural activity, the reduction in the size of the CAPs was rapid and complete. On no occasion in these experiments was the material found to have only a partial effect on the CAP (i.e. it appeared to be an all or none effect).

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