The treatment of large ulcerating facial haemangiomas associated with PHACE syndrome is a challenge. Timolol has previously been used for small uncomplicated haemangiomas. A pilot study of small uncomplicated infantile haemangiomas in six patients showed improvement with 0·5% timolol maleate gel, applied for an average duration of 3·3 months.[8]

Early effects of beta blockers that occur within 1–3 days after the start of therapy are due to vasoconstriction; intermediate effects are due to the blocking of proangiogenic signals, including vascular endothelial growth factor, basic fibroblast growth factor and matrix metalloproteinase, resulting in growth arrest; and long-term effects are due to induction of apoptosis in proliferating endothelial cells, resulting in tumour regression.[9,10] Hence timolol is potentially useful in reducing progression and hastening resolution of progressive or noninvoluting haemangiomas.

Our patient showed a dramatic response to topical timolol 0·5% ophthalmic lotion applied over the haemangiomas. There was a decrease in redness within 3 days and almost complete resolution of the haemangiomas by 8 weeks. Pruritus was the only side-effect observed after 4 weeks of application. Close clinical monitoring did not show adverse effects suggestive of systemic absorption of a beta blocker.

The systemic bioavailability of ocular timolol in healthy volunteers is about 50%, while systemic absorption following topical application has not been studied. This will depend on the thickness and size of the haemangioma and hence the drug should be used with close monitoring of systemic side-effects. Adverse reactions reported with ocular timolol for paediatric glaucoma include drowsiness, bradycardia, itching sensation in the eyes, Cheyne–Stokes breathing, apnoeic spells and multiple severe asthma exacerbations.[11] Hence it should be used with caution in children with cardiorespiratory disorders.

Thus topical application of timolol is a safe and highly cost effective technique for the management of infantile haemangiomas and can be particularly useful in children with PHACES syndrome, where oral propranolol may be contraindicated. The availability of topical formulations that are effective with minimal systemic absorption will make the topical application of timolol a first-line therapy and treatment of choice for the management of haemangiomas in the future.

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Local anaesthetic preparation in dermatological surgery: a labour- and time-efficient approach

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MADAM, The administration of local anaesthesia is fundamental to the practice of dermatological surgery. Furthermore, achieving effective anaesthesia in as 'pain-free' a manner as possible is desirable for both operator and patient. Given the high volume of dermatological surgical procedures performed in day-case and outpatient facilities on a daily basis, preparing local anaesthetic solutions in a timely and effective manner has the ability to contribute significantly to the provision of an efficient dermatology service.

Lidocaine with adrenaline is one of the commonest local anaesthetic preparations used. The presence of adrenaline is associated with a prolonged anaesthetic half-life, reduced toxicity and local vasoconstriction. However, premixed lidocaine with adrenaline has a pH of 3·5–5·5 and is painful on injection for the vast majority of patients. Warming of local anaesthetic solution to 37 °C and buffering with sodium bicarbonate to neutralize the pH of the solution have been shown to result in less discomfort during administration.[1,2] As a consequence, it is our practice to add sodium bicarbonate to our local anaesthetic solutions.

Although dermatological surgery is associated with a low rate of postoperative wound infections, when infections do occur they can have a significant effect on the cosmetic and functional outcome of a procedure. The administration of

intra-incisional antibiotic treatment has been shown to be associated with a lower incidence of postoperative wound infection.[3] It has the benefit of localizing the antibiotic to the susceptible site.

Twenty-millilitre vials of premixed lidocaine with adrenaline are readily available and in our collective experience are used regularly by dermatology departments globally. The addition of a buffering agent to individual 20-mL vials can be a time-consuming and labour-intensive process. Furthermore, should the surgeon wish to add antibiotic prophylaxis to the solution, the small volume of antibiotic required to give the desired bactericidal effect would be difficult to dispense accurately and reproducibly.[3]

Gram-positive organisms, in particular staphylococci and streptococci, account for the vast majority of microorganisms implicated in cutaneous wound infections. The macrolide antibiotic clindamycin is not only effective against such microorganisms but has the added advantage of utility in penicillin-allergic patients.

We therefore describe an efficient method of preparing 'buffered' local anaesthetic solution with antibiotic prophylaxis (if so desired) for use in dermatological surgery. Twenty millilitres is withdrawn from a 100-mL bag of normal saline and discarded. One hundred millilitres of 1% lidocaine with adrenaline 1 : 200 000 (5 × 20 mL vials), 20 mL 8·4% sodium bicarbonate and 0·6 mL clindamycin (150 mg mL^{-1}) are added to the bag containing the residual 80 mL of normal saline. The total volume of 200·6 mL fits comfortably within the bag (Fig. 1). This results in a local anaesthetic solution containing 0·5% lidocaine (i.e. 5 mg mL^{-1}), adrenaline 1 : 400 000 and 450 μg mL^{-1} clindamycin. The solution is labelled and dated. It is refrigerated at 4 °C and any unused solution is discarded after 4 weeks (although in practice given the high volume of surgery performed by most dermatology units such as ours, in our experience a new bag of local anaesthetic is required at least every alternate day). There are data demonstrating that buffered solutions of lidocaine and adrenaline maintain adequate efficacy for up to 1 week at room temperature and up to 4 weeks if refrigerated.[4,5] On a daily basis, 1, 3, 5 and 10 mL volumes are withdrawn into labelled syringes under aseptic conditions (Fig. 2). Any syringe which is not clearly labelled is discarded without use. Depending on the extent of the surgical procedure, the appropriate sized syringe(s) is/are selected and anaesthetic infiltrated. The syringe is then discarded. This 'single use' approach is designed to minimize the risk of sharps injuries and for choosing the correct sized syringe aimed at reducing waste. (In order to prevent possible contamination of the anaesthetic-containing syringes, should additional anaesthetic be required the operator may pick it up themselves, having changed their gloves beforehand, or they can ask an assistant).

The solution we describe has a concentration of 0·5% lidocaine with adrenaline 1 : 400 000. It has been our experience of over 10 000 dermatological surgical procedures that this concentration of lidocaine achieves satisfactory local anaesthesia in our patients. The advantage of using a lower concentration of lidocaine becomes apparent when undertaking larger or more prolonged procedures such as tumour extirpation utilizing Mohs micrographic surgery requiring extensive reconstruction. In addition, using a more dilute concentration, one is less likely to reach the proposed toxicity level of locally infiltrated lidocaine with adrenaline (7 mg kg^{-1}).

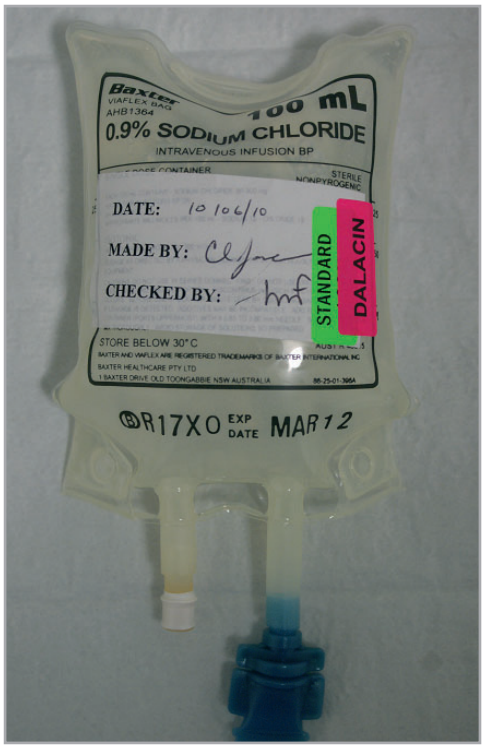

Fig 1. Prepared 'buffered' local anaesthetic solution. A total volume of just over 200 mL is achieved, comprising 80 mL normal saline, 100 mL 1% lidocaine with adrenaline 1 : 200 000, 20 mL 8.4% sodium bicarbonate and 0.6 mL clindamycin (150 mg mL^{-1}) referred to as our 'standard' preparation. The bag having been checked by two clinical members of staff is clearly labelled with the date of preparation, and is readily identified as also containing antibiotic.

Fig 2. Various volumes of local anaesthetic may be withdrawn. Note that each syringe is clearly labelled as to whether it contains antibiotic (pink label) or no antibiotic (green label) for use in cases of antibiotic drug allergy, for example. Any syringe without a label is discarded.

It is our personal practice to utilize the antibiotic-containing local anaesthetic in all our surgical procedures given that we routinely perform large numbers of complex reconstructions at our institution. Individual surgeons may, however, prefer to reserve the use of intra-incisional antibiotic for higher-risk groups such as diabetic patients or the elderly or in prolonged surgical reconstructions. Given the small quantities of antibiotic used, coupled with the method of delivery, in our experience antibiotic resistance has not been a problem.

We have found the use of a buffered lidocaine solution (with the addition of intra-incisional antibiotic if so desired) to be safe, convenient and effective during dermatological surgery. We thus describe what we believe to be an efficient, labour-saving method of preparation. Given the ongoing financial constraints globally and within the National Health Service in the U.K., any method of maximizing efficiency and, as a consequence, productivity (without compromising the standard of care received by our patients) should be given careful consideration.

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No major role for glutathione *S*-transferase gene polymorphisms in sensitization to *para*-phenylenediamine and other xenobiotics: a study of association and a meta-analysis

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Madam, *para*-Phenylenediamine (PPD), an important contact allergen, may cause severe allergic contact dermatitis (ACD). PPD is susceptible to auto-oxidation, resulting in reactive oxygen species (ROS) formation.[1] It has been found that oxidative stress from ROS may play an important role in the sensitization phase of ACD to PPD.[1] Glutathione *S*-transferases (GSTs) are known for their detoxifying role through scavenging ROS.[2] However, human GST genes display polymorphisms which are likely to contribute to interindividual differences in responses to xenobiotics.[3] By performing an association study as well as a meta-analysis, we examined the role of GST polymorphisms in sensitization to PPD and other xenobiotics. Entire gene deletion results in the null-alleles *GST (theta) T1*0* and *GST (mu) M1*0*, subsequent absence of enzymatic activity and therefore, 'high risk'. For the GST pi-1 gene (*GSTP1*), a single nucleotide A to G substitution at position 313 is known.[4] The most common *GSTP1*313AA* was taken as the reference allele. To determine a possible synergistic effect, the combined *GSTT1/GSTM1* genotype was considered. Genotyping was performed by a real-time polymerase chain reaction (PCR) assay. The association analysis used a German case–control set, containing 150 cases and 202 controls. After approval by the ethics committee, participants gave written informed consent. For meta-analysis we identified two papers. Wang *et al.* (2007) studied sensitization to chromate, whereas Westphal *et al.* (2000) examined sensitivity to thimerosal.[5,6] Although these studies concern different xenobiotics, we assumed that they follow the same detoxification pathway.[5,6] Including those in our study we analyzed 251 patients with sensitivity to a xenobiotic (PPD, chromate or thimerosal) and 503 control subjects altogether. *GSTT1*0* was significantly more frequent in controls (22·5%) compared with sensitized subjects (13·5%), yielding an odds ratio (OR) of 0·54 [95% confidence interval (CI) 0·30–0·96, $P = 0·04$] (Table 1). Neither *GSTM1*0*, nor *GSTT1*0/GSTM1*0* was significantly associated with sensitization to PPD (Table 1). *GSTP*313* genotypes were not significantly different in sensitized subjects compared with controls (Table 1). In the meta-analysis no significant relationship was found either between *GSTT1*0* or *GSTM1*0*, or between *GSTT1*0/GSTM1*0* and sensitized subjects (Fig. 1).

Contrary to our *a priori* hypothesis we observed a protective effect for *GSTT1*0*. This finding is in contrast to that reported by Westphal *et al.* (2000) and Wang *et al.* (2007) who observed *GSTT1*0* more frequently in sensitized subjects.[5,6] To accommodate this variation across different studies, we performed a meta-analysis, which found no association of *GSTT1*0* and sensitization overall (Fig. 1). For *GSTM1*0*, both we and Wang *et al.* (2007)[5] found no association with sensitization (Table 1). In contrast, Westphal *et al.* (2000)[6] found *GSTM1*0* significantly more frequent among sensitized subjects. Meta-analysis of all three studies found no difference in the frequency of *GSTM1*0* between sensitized subjects and controls (Fig. 1). Our association study on the *GSTP1* polymorphism and sensitization to PPD yielded no statistical relationship (Table 1); possibly due to the controls deviating slightly from Hardy–Weinberg equilibrium (HWE) ($P = 0·02$). For 'high-risk' profiled patients, i.e. *GSTT1*0/GSTM1*0*