

This position statement is for general information and discussion only and is not intended as medical advice. Its purpose is to review the current literature on a controversial subject so as to assist medical practitioners who have an interest in pain management. The epidural injection of depot corticosteroids is one of a number of treatment techniques for chronic pain, and it is the view of the directors of the Australian Pain Society Limited that patients with chronic pain require assessment and treatment within multi-disciplinary pain management programmes. This statement does not encourage or discourage medical practitioners from utilising epidural steroid injections as one treatment modality. While this review of the pertinent literature may be of assistance to practitioners, no responsibility can be accepted by the Australian Pain Society Ltd., or its directors, for any inaccuracy contained in studies referred to therein. All liability is expressly disclaimed for any loss or damage which may arise from any person acting on any statement or information contained herein.

## INTRODUCTION

The Board of Directors of the Australian Pain Society Inc. Recently considered the controversy which has arisen following the widely publicised claims that the epidural administration of methylprednisolone acetate (marketed under the tradename of Depo-Medrol up Upjohn Pty Limited) had caused serious adverse effects.

Among the claimed adverse effects which had been reported in the media, have been allegations that epidural administration of methylprednisolone acetate had caused patients to become “physical wrecks” who “faced a lingering living death,” and that some “had become pain-ridden invalid pensioners.” It has also been claimed that injections of methylprednisolone acetate by this route had led to brain damage and had caused death, and that patients who have had this treatment will become paralysed and incontinent within a three to four-year period following the injection as a consequence of spinal arachnoiditis.

This Society has previously expressed support “in principle, with some reservations” for the epidural administration of depot corticosteroids. In a statement published in October 1983, which had been prepared by a committee of the Society, the Australasian Pain Society (as it was then) stated that “provided the epidural route of administration is used and that routine care and aseptic techniques are followed, then neurological sequelae will be avoided. The committee does not support the general use of despot-corticosteroids intrathecally nor excessive use of these agents epidurally.”

A review of published studies of the use of epidural corticosteroid agents for sciatica, which appeared in 1985,<sup>2</sup> concluded that “analysis of the literature attests to the safety of the procedure.” The authors of this review comment that adverse effects occur with intrathecal injections, and that “the complications of epidural corticosteroid agents are neither more frequent, nor worse, than those of other procedures used in the diagnosis and treatment of spinal pain, and indeed, are arguably more benign in many cases.”

With regard to efficacy of epidural steroids, the review concluded that “the literature is less definitive.” It was suggested that epidural injections of corticosteroid agents are of value in the treatment of patients with pain or relatively short duration due to radiculopathy, and it was noted that this is “in accord with the proposed anti-inflammatory rationale for the use of epidural corticosteroid injections.” However, the authors cautioned that no controlled studies of acute pain patients treated with epidural corticosteroids had been reported, and that “the possibility of spontaneous resolution looms strongly in patients with histories of less than two to four weeks’ duration.”

## CONTROLLED TRIALS

Special note should be made of comparison and controlled trials of epidural steroids. Beliveau compared epidural injections of procaine alone with injections of procaine plus methylprednisolone in the treatment of unilateral

sciatica.<sup>3</sup> There were 24 patients in each group, and the response was assessed at follow-up from one to three months after treatment.

The author reported that about 70 percent of patients reported improvement, irrespective of which type of injections was administered. However, those patients who had a history of sciatica longer than one month showed a better response following injection of procaine plus steroid. Beliveau commented that among the patients with “a long history of severe pain” the injection of procaine together with methylprednisolone “was found beneficial in almost all cases.”

A controlled double-blind trial of epidural methylprednisolone for the treatment of unilateral sciatica associated with lumbar disc disease was reported by Dilke et al.<sup>4</sup> A total of 100 patients were included in the study; they were allocated at random to the “treated’ or “control” group. Those in the “control” group were given “a superficial injection into the interspinous ligament of 1ml of normal saline.” The treated group showed a significantly greater pain relief than the controls; the treated group also showed a significantly greater rate of early return to work.

The authors commented that “several thousand extradural corticosteroid injections have been carried out in this department, and our findings are in agreement with those of other workers - that the procedure is entirely safe, provided careful attention to asepsis is observed’

Snoek et al.<sup>5</sup> reported on a double-blind study, involving 51 patients, comparing epidural methylprednisolone acetate injections with injections of normal saline. All the patients in this study had symptoms, signs and radiological abnormalities consistent with lumbar disc herniation and nerve root compression. The authors found that there was no significant differences in outcome between the two groups, and that at follow-up a mean of 14 months after treatment, more than 50 percent of patients in both groups had undergone surgical treatment.

It would appear that many of the patients included in this study, with confirmed radiological signs of disc herniation and nerve root compression, were suffering from a significant degree of pressure on the nerve root, the severity of which made surgery inevitable.

Yates compared the effects of epidural injection of normal saline, 0.5 percent lignocaine, triamcinolone hexacetonide, and a combination of lignocaine and triamcinolone.<sup>6</sup> The injections were given at weekly intervals in random order, each patient being given the series of four injections. Patients who improved before completion of the four injections were removed from the trial.

There were 20 patients in this study. Outcome was assessed by measuring change in straight leg raising and lumbar spine mobility, and by subjective reports of improvement. The author concluded that “greatest improvement was noted after the injection containing steroid.”

In another double-blind study which compared procaine with methylprednisolone administered by epidural injection, Cuckler et al included 73 patient with radiologically confirmed lumbar nerve root compression consistent with acute disc herniation or spinal stenosis.<sup>7</sup> They reported that there was no statistically significant difference in response between the control and the experiment groups.

The comments made above with respect to the study by Snoek et al. also apply to this trial, as patients with radiologically demonstrated nerve root compression have a mechanical lesion which is unlikely to respond to the anti-inflammatory effects of the steroid administered by epidural injection. It is also noteworthy that Cuckler et al. performed the injections at the L<sub>3</sub>-L<sub>4</sub> level, which was at a higher level than the site of most lumbar disc lesions. The efficacy of the injections was evaluated after 24 hours, which is too early for any benefit to become apparent.

## CLINICAL STUDIES

Pawl et al. also evaluated the role of epidural steroids in the management of pain resulting from degenerative disk disorders, including radiculopathy from herniated disks.<sup>8</sup> They reported on a series of 247 patients treated with this technique. Of these, 103 patients had neck pain; the other patients had low back pain. The authors showed that 50% of patients with cervical radicular syndromes and 30% of patients with lumbar radicular syndromes were able to avoid surgery with the help of epidural corticosteroid injections. Although they expressed disappointment with these results, Pawl et al. concluded that “epidural steroid injections have also proven of therapeutic benefit in those patients whose cervical or lumbar spondylosis syndromes are not associated with significant radiculopathy, and thus would not be considered for surgical intervention. The lack of significant complications in this series bespeaks the benign nature of the treatment.”

The use of epidural injections of methylprednisolone acetate in the treatment of post-herpetic neuralgia and post-traumatic neuralgia was described by Forrest.<sup>9</sup> A total of 63 patients were included in this study. Patients were treated with three injections given at one week intervals. Follow-up after one year showed that 89% of patients in the post-herpetic neuralgia group were pain free, as were 59% of patients in the post-traumatic pain group.

The author commented that “side effects were minor in all cases.” The most frequent side effects noted were mild weight gain and “elevation of affect.” A total of 252 injections were given (this total included epidural steroids and diagnostic local anaesthetic blocks), and complications included puncture of the dura on three occasions, a blood tap on two occasions, and spinal headache associated with dural puncture on one occasion. Hypotension was recorded with local anaesthetic blocks only.

Warfield and Crews reported on a study of 187 patients with lumbar radiculopathy treated with epidural injections of 1% lidocaine and 80mg of methylprednisolone acetate.<sup>10</sup> Injections were repeated up to a total of three in a six-month period, depending on the initial response.

In the analysis of outcome, improvement of these patients was related to whether or not the pain complaint was work related. A total of 102 patients (out of the 161 who responded to follow-up one to three years after treatment) claimed improvement following the injection. The authors of this study made no mention of side effects or complications following the epidural injections, which could be interpreted as an indication that any adverse effects noted were insignificant.

Cicala et al. Reported on 204 cervical epidural injections of corticosteroids, in the treatment of 142 patients with neck pain over a one year period.<sup>11</sup> Methylprednisolone acetate was the steroid used, and this was combined with 1.5 % lidocaine. This study was specifically concerned with side effects and complications of cervical epidural steroid injections.

Four complications occurred: in two cases the dura was punctured (without any adverse sequelae), there was one episode or transient bilateral upper extremity weakness, and one episode or nausea and vomiting which lasted for 12 hours. The most frequent side effects were stiff neck lasting 12-24 hours, which occurred in 13.2 % of patients, and mild facial flushing which occurred in 9.3% of patients.

The authors concluded that “in this large series, the procedure appears safe to use in a outpatient setting.”

The arguments for<sup>12</sup> and against<sup>13</sup> the use of epidural steroids are presented in the Newsletter of the American Society of Regional Anaesthesia in September 1989. In arguing against the use of epidural steroids, Hammonds expresses the following concerns:

“I oppose the widespread practice of using the method routinely in all patients with back pain... I oppose the use of epidural steroids without adequate evaluation of every patient before treatment. I oppose the growing insistence by many practitioners that epidural steroids are a “proven remedy” for back pain. I oppose the claim by many academicians that this therapy has already been proven and that further study is unwarranted.”<sup>13</sup>

Among the complications listed by Hammonds were “transient complaints” such as back pain, headaches, and leg pain. Adverse effects of steroid administration which have been reported include water retention, skin lesions, and Cushing’s syndrome.<sup>14</sup> Hammonds also noted that cardiovascular complications can occur, as well as complications due to accidental dural puncture or infection.

The combination of epidural methylprednisolone and morphine has been advocated for the treatment of persistent low back pain following laminectomy.<sup>15</sup> A more recent study, in which triamcinolone rather than methylprednisolone was used, failed to show any benefit from the combination for the two agents.<sup>16</sup> In this study, significant ventilatory depression occurred in a significant proportion of patients given epidural morphine.

In view of the current controversy in this country over the use of epidural steroids, it was of interest to note several presentations on this subject at the recent 6th World Congress on Pain held in Adelaide during April 1990.

Cervical steroid epidural blocks were used for treatment of symptoms due to herniated discs, and were found to provide sustained pain relief for 84 percent of the 61 subjects (out of 93 patients) contacted during the follow-

up.<sup>17</sup> The authors noted that “the procedure is safe, convenient and generally well accepted by patients.”

Two other presentations reported on a group of 212 patients treated with lumbar epidural steroids; 114 patients (53.8%) obtained a satisfactory result.<sup>18</sup> Best results were achieved by patients with radiculopathy (52.8% satisfactory pain relief), whereas patients with other diagnoses were less likely to improve (21.7% success rate). There was a reduction in pain severity as well as sleep disruption, and significant numbers of patients returned to employment.

The same authors reported on factors which contributed to outcome following treatment with lumbar epidural steroids, and concluded that pain duration and pain severity, sleep disruption, level of education and employment were all likely to affect treatment outcome.<sup>19</sup>

The steroid used by Abram and Hopwood was triamcinolone diacetate (Aristocort Intralesional) combined with 1% lidocaine (personal communication, 1990). However, the most commonly used depot corticosteroid preparation for epidural injection has been methylprednisolone acetate (Depo-Medrol). The recently published study by Cicala et al. is therefore of particular importance, as these authors investigated the effects of methylprednisolone acetate on meningeal membranes and nervous tissue.<sup>20</sup>

Epidural injections of methylprednisolone acetate and 1% lidocaine were administered to healthy adult rabbits, and the study included control groups. The animals were killed either on day 4 or day 10 following injection, and both gross and microscopic examination of the area of injection was made.

There was no evidence of meningeal thickening or white cell infiltrates in animals which had been injected with the lidocaine and methylprednisolone acetate. The authors concluded that this study indicated that there is no

significant irritation and inflammatory reaction following the injection of these agents into the epidural space. Cicala et al. noted, however, that the sample group was small and therefore the findings should be interpreted with caution. They also noted that there was a possibility that other species may react differently, and that there was also the possibility of individual sensitivity to the agents injected into the epidural space.

In an extensive review. Benzon commented that complications of epidural steroid injections are rare.<sup>21</sup> He noted that epidural steroid injections have been reported to be therapeutic in conditions such as herniated nucleus pulposus with either nerve root compression or nerve root irritation, and in cases of spondylolisthesis if nerve root irritation is present. Epidural injections of steroid are unlikely to be of significant therapeutic value in other conditions causing back pain, but may hasten recovery in patients with annulus tears.

Based on the relevant scientific literature which has been published since 1983, the Board of Directors of the Australian Pain Society Inc. is of the view that the epidural administration of corticosteroids is a potentially valuable treatment technique in the management of some patients with radicular pain of recent onset. Such treatment should be undertaken only by suitably trained practitioners, experienced in the administration of epidural injections. Provided that the injection is given into the epidural space and not intrathecally, there is no convincing evidence that this procedure carries any significant risks to the patient, either of immediate complications or long term adverse effects.

#### ADVERSE EFFECTS

We are aware of the series of articles and letters by Dewey A. Nelson, published since 1973, claiming that “intraspinial” injections of methylprednisolone acetate produce spinal arachnoiditis due to the putative toxic effects of polyethylene glycol.<sup>22-29</sup> Nelson recently repeated these claims in a television programme, in which he asserted that such injections

will produce paralysis and incontinence within a period of about four years, due to spinal arachnoiditis. Our review of the relevant literature has shown that there is no basis for this assertion.

The findings by Cicala et al.<sup>20</sup> that there were no indications of tissue reaction to the epidural injection of methylprednisolone acetate in rabbits has been noted above.

In the article published in 1988 in the journal "Archives of Neurology," Nelson<sup>26</sup> quoted studies by Margolis et al.,<sup>30</sup> Hurst,<sup>31</sup> Chino et al.<sup>32</sup> and Selby<sup>33</sup> in support of his claims about the toxic effects of polyethylene glycol. As noted by Wilkinson<sup>34</sup> in a subsequent Letter to the Editor, Nelson had misquoted each one of these studies.

Nelson referred to nine patients who had developed arachnoiditis following intrathecal injections of methylprednisolone acetate and who had been described in several articles of which he had been a co-author; he assumed that these injections had been the cause of arachnoiditis without discussing other possible aetiological factors. He then extrapolated the "dangers associated with the intrathecal use of methylprednisolone acetate" as seeming "to apply well to each anatomical space around the spinal cord, due to anatomical contiguity as well as to technical errors of injection."

In that particular article, Nelson claimed that epidural needle placement is inaccurate in 42.5% of patients; in response to the letter by Abram,<sup>35</sup> Nelson conceded that this was an inflated figure "due to typographical error." He then noted that injections into ligaments are quoted by some authors as occurring in 25% of cases, with the rate of accidental spinal taps varying between 0.5% and 2.5%.

In that letter Abram noted that in a series of about 4,000 epidural steroid injections using mainly triamcinolone diacetate (which contains the same concentration of polyethylene glycol as methylprednisolone acetate) over a

13 year period “there have been no serious reactions to the procedure during that time.”

In another large series, Delaney et al. reported on 6,000 epidural steroid injections with triamcinolone diacetate, with only two complications, neither due to neurotoxicity or meningeal reaction.<sup>36</sup>

Cronen and Waldman recently reported on a group of 48 patients treated with cervical steroid epidural nerve blocks, using methylprednisolone and bupivacaine, for treatment of intractable tension-type headaches.<sup>37</sup> follow-up over a three month period showed a significant reduction in the average pain score. The authors commented that “no side effects other than transient soreness at the injection site were noted, and no complications occurred.”

The instillation of methylprednisolone acetate directly onto the exposed nerve root during laminectomy was described by Davis and Emmons in a series of 43 patients.<sup>38</sup> The results were compared with a control group of 43 patients; the group treated with the steroid showed a significantly shorter hospital stay associated with less severe postoperative pain, and less postoperative muscle spasm.

It is also relevant to note Australian publications on the use of epidural steroids in the management of low back pain and sciatica. Ryan and Taylor reported on 108 patients who presented with a clinical diagnosis of acute lumbar disc prolapse and nerve-root pain.<sup>39</sup> The patients were treated with epidural or intrathecal methylprednisolone acetate. Patients with pain duration of less than four weeks had a favourable response in 75% of cases; for patients with pain of longer than six weeks duration, the response rate was 43%. The authors commented that the treatment was more likely to be effective when the patients was male, the duration of symptoms was less than four weeks, and the patient had “irritation rather than compressive neuropathy.”

Following subsequent correspondence, Ryan and Taylor stated that they were continuing to use Depo-Medrol by epidural injection only.<sup>40</sup>

Bradley et al., writing in the Correspondence columns of *The Medical Journal of Australia*, stated that over the previous ten years they had used epidural Depo-Medrol “for the treatment of lumbar intervertebral disc prolapse in more than 10, 000 patients.”<sup>41</sup> They commented that side effects encountered had included an increase in post-injection pain and headache, described as “relatively minor, uncommon and transitory.”

Corrigan et al. reviewed the literature on intraspinal corticosteroid injections, which reported on a total of some 10,000 patients.<sup>42</sup> They commented that “despite these large numbers, major complications have been excessively rare.” The complications which had been reported included infection, hypersensitivity reactions, headache, and pain at the site of injection.

The clinical trials reviewed in that paper included some 3,000 patients, with improvement in 63% to 100% of “acute cases.” According to Corrigan et al., the improvement was obtained in an average of 75% of patients. The authors concluded that “an extradural injection of corticosteroid for acute lumbar radiculopathy is safe, effective and side effects are remarkable uncommon. It shortens the time of recovery from severe pain, avoids prolonged bed rest or hospitalisation, allows earlier mobilisation and physiotherapy, and may avoid the need for surgery. On current evidence, it should continue to be used to treat this condition.”<sup>42</sup>

We note that the Guidelines for *Medical Practitioners for the Epidural Administration of Depo-Medrol*,<sup>43</sup> issued by the Health Department of Western Australia, have examined in considerable detail the relevant literature, and concluded that there are specific indications for epidural steroids, as well as contraindications. In relation to the claims that the use of methylprednisolone acetate causes arachnoiditis as a consequence of

the tissue reaction to polyethylene glycol if inadvertent intrathecal injection occurs, the *Guidelines* note that a number of other causes of that condition may be implicated, including the original trauma. (Incidentally, this document incorrectly states that the 18 patients described by Roche<sup>44</sup> developed arachnoiditis following epidural injection of Depo-Medrol. The article clearly states that in all cases the injection had been intrathecal.)

It is relevant to note that the literature on spinal arachnoiditis includes documented cases of this condition in patients with lumbar disc lesions<sup>45</sup> or spinal stenosis<sup>46</sup> who had not been subjected to myelography, spinal injections, or surgery. It has also been recognised that chronic spinal arachnoiditis may develop without any apparent cause<sup>47</sup> (termed idiopathic spinal adhesive arachnoiditis by Shikata et al.<sup>48</sup>) and a familial type of this condition has also been described.<sup>49</sup>

## CONCLUSION

It needs to be emphasised that before any patient is treated by injection of epidural steroids, the treating physician must obtain the patient's consent, based on a thorough discussion of the nature of the treatment and its possible benefits and risks. For some patients the benefits to be obtained from epidural steroid injection mean that spinal surgery can be avoided, and thus the patient avoids exposure to the risks and morbidity associated with major surgery.

Whilst the Board of Directors of the Australian Pain Society is aware that the manufacturers of Depo-Medrol, Upjohn Pty. Limited, no longer recommend or support the use by epidural injection of that agent. It is our view that this action by the manufacturers reflects concern about the possibility of litigation over alleged adverse effects of Depo-Medrol administered by this route rather than being due to any demonstrated significant adverse effects of this mode of treatment. The announcement by that company published in December 1990 in the *Medical Journal of Australia* does not, in our view, accurately reflect the demonstrated efficacy and safety of

methylprednisolone acetate when administered by the epidural route by suitably trained and experienced practitioners. The manufacturers of another depot steroid, Schering-Plough, have similarly issued a statement in which it was emphasised that “under no circumstances do we recommend that Celestone Chronodose be administered by epidural injection.”<sup>51</sup> A very similar statement has also been made by David Bull Laboratories,<sup>52</sup> manufacturers of injectable dexamethasone sodium phosphate.

In 1983 Upjohn unsuccessfully applied to have Depo-Medrol approved for epidural administration, but this was rejected by the Australian Drug Evaluation Committee. The company has not made public any material which would justify their about-face on the question of the epidural administration of Depo-Medrol.

This situation is this analogous to the withdrawal from the market of Debendox in response to litigation over the alleged teratogenic effects, despite the absence of valid scientific data showing a link between Debendox and congenital birth abnormalities.

It is also a matter of concern that medical defence associations have been reported as refusing to provide cover for members who continue to administer epidural steroids. This has been apparently the attitude taken by the Medical Association in Western Australia.<sup>53</sup> However, the Australasian secretary of the Medical Protection Society has cautioned that medical indemnity organisations should not “pre-judge issues, but examine each request for assistance individually.”<sup>54</sup> We endorse his comment that the practitioner ensure “that there be sufficient contemporaneous recording of the consultation to document the nature of the information discussed with the patient, to make it very clear that ‘potential risk, benefits and limitations’ of the treatment were discussed in full,” and that if the practitioner considers that there is a specific indication for epidural steroid injection this should be discussed with the patient and the treatment administered if the patient

consent is obtained after all the relevant considerations have been canvassed.

Similarly, the Australasian secretary of the Medical Defence Union has stated that members of the MDU would be “assisted in the usual way” if sued by a patient alleging injury from epidural steroid injection.<sup>55</sup>

The Medical Defence Association of South Australia has recommended that if epidural steroid injection is advised to a patient, a specific protocol be followed by the treating practitioner in providing the patient with all the relevant information and that this be documented and a consent form confirming that this had been done be signed by the patient.

In our opinion, epidural steroid injection is a valuable technique in the management of selected groups of pain patients. It is a matter for regret that inaccurate comments have been recently given wide media publicity with respect to this treatment modality. This has now led to solicitors touting for clients with newspaper advertisements in which the name DEPO MEDROL is featured in large print. Chronic pain is a multifaceted problem which also involves significant physiological, economic and social determinants,<sup>56</sup> and it is both simplistic and inaccurate to attribute to one specific event the continuation of chronic pain complaints, and any alleged resultant disability. Epidural steroid injection is one procedure within a multidisciplinary approach to pain management, and in the best interests of adequate and comprehensive patient care it should be available for those patients who are considered by their treating practitioners to be likely to benefit from this procedure.



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