REVIEW ARTICLE

The Value of "Multimodal" or "Balanced Analgesia" in Postoperative Pain Treatment

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Treatment of postoperative pain is provided for humanitarian reasons and to alleviate nociception-induced responses, such as the endocrine metabolic response to surgery, autonomic reflexes with adverse effects on organ function, reflexes leading to muscle spasm, and other undesirable results (1).

During the last decade there has been a virtual explosion in our knowledge of basic pain physiology (2,3), but the implications for clinical practice have been less substantial. The explanation for the discrepancy between the fast progress in basic pain pathophysiology and the rather slow advances in providing optimal postoperative pain treatment may be several, but one important factor may be that more than 95% of the literature on postoperative pain treatment has considered unimodal treatment. We have emphasized previously that total or optimal pain relief allowing normal function can not be achieved by a single drug or method without major strain on equipment and surveillance systems or without significant side effects (4). Therefore, we have recommended combined analgesic regimens (balanced analgesia) or a multimodal approach to the treatment of postoperative pain (4). The rationale for this strategy is achievement of sufficient analgesia due to additive or synergistic effects between different analgesics, with concomitant reduction of side effects, due to resulting lower doses of analgesics and differences in side-effect profiles.

We summarize here the existing knowledge concerning the efficacy of analgesic combination therapy from postoperative pain studies. The effects on postoperative outcome are not included, because of lack of sufficient studies. We also exclude obstetric and pediatric pain, which may represent special pain entities and solutions for treatment, although they obviously share many of the problems of general postoperative pain. Primary emphasis will be placed on moderate and severe pain and the use of and need for prolonged, continuous, or intermittent regimens. Thus, single-dose combination therapy will not be discussed unless vital to interpretation and to understanding future approaches to prolonged combination therapy. We also did not review efficacy data from single modality treatments, because these have been reviewed elsewhere.

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Background

Figure 1 shows the pathways of nociceptive stimuli, including those conducting pain, from the site of surgical injury passing through the peripheral nervous system to the central nervous system. At present, several techniques are available to treat pain: at the peripheral level using local anesthetics, nonsteroidal antiinflammatory drugs (NSAID), opioids, or other analgesics; peripheral nerve blocks with local anesthetics and α_2-adrenergic agonists; at the spinal cord level using local anesthetics, opioids, α_2-agonists or other analgesics; at the cortical level using opioids or other analgesics; and, finally, a combination of these techniques.

In the following, data on the efficacy and side effects of combination therapy, compared with unimodal therapy, are discussed with an emphasis on pain relief during function, such as cough and mobilization, rather than merely during rest.

Peripheral-Acting Analgesics

Local Anesthetics

Local anesthetics have been used for several decades for wound infiltration, but their application and efficacy has been documented mostly in relatively minor or moderate procedures (5). The effect on postoperative pain is rather short-lasting, emphasizing the severe need for more long-acting drugs (5). There are few studies that evaluate the efficacy of combining other analgesic therapy with the administration of local anesthetics. This is unfortunate, because a combined peripheral attack on pain seems rational.

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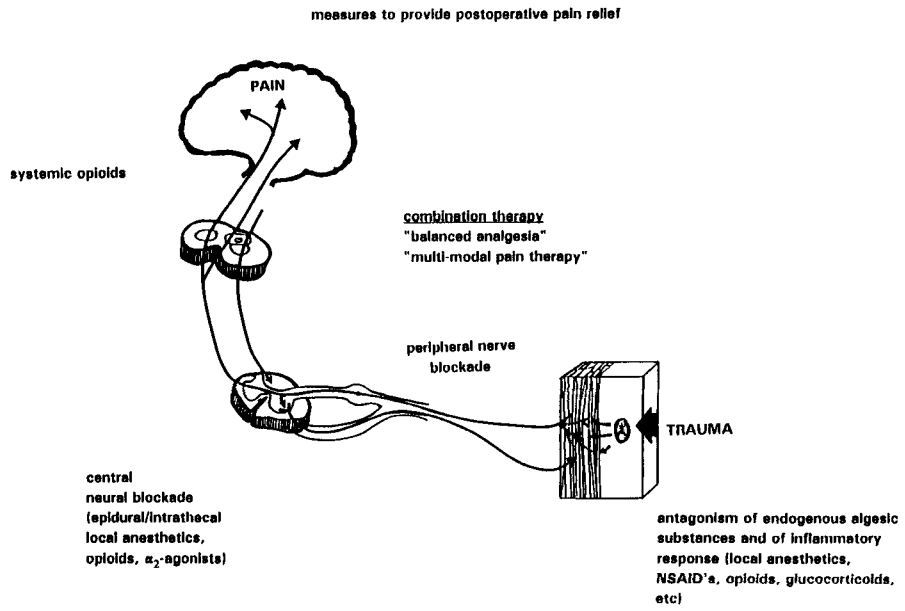

Figure 1. Measures to provide pain relief.

Peripheral Opioid Instillation

Some clinical studies recently have demonstrated peripheral instillation of morphine to reduce postarthroscopic pain (6–10). The analgesic effect probably is mediated through inflammatory-induced novel appearance of opioid receptors at the peripheral nerve endings (11). The efficacy of combining intraarticular local anesthetics and opioids may be important, but so far, the experience has been discordant (8,10).

Nonsteroidal Antiinflammatory Drugs (NSAID)

The value of NSAIDs in minor, moderate, or severe postoperative pain is well documented (12,13), but their efficacy is too small to be the sole analgesic in more severe pain states, although they represent an ideal alternative component in the multimodal approach to postoperative pain treatment. Additive or synergistic effects of combining NSAID with systemic opioids are well documented in minor surgery (14–16), but most combination studies of NSAID and opioids have aimed to demonstrate the ability of additional NSAID to reduce the amount of opioid, resulting in a similar degree or only slightly improved pain relief (12,13). Although this approach may be valuable for minor procedures, such as laparoscopy, with subsequent reduction of opioid-induced side effects (nausea, vomiting, sedation), a fixed-dose combination therapy theoretically should enhance the analgesic potency that is necessary in moderate or major surgery. So far, only one such study is available. It demonstrates improved analgesia by fixed-dose combination with piroxicam and opioid after total hip replacement (17). The combination of systemic NSAID with a central neural block with bupivacaine and/or opioids has been studied in major abdominal (18) and thoracic surgery (19), in which additional treatment with piroxicam 20–40 mg daily did not improve analgesia during rest, cough, or mobilization during an otherwise effective epidural low-dose bupivacaine-opioid regimen. Further studies of such triple combination therapy, especially in soft- and bone-tissue trauma such as orthopedic procedures are needed. After cesarean section the combination of low-dose epidural morphine and intramuscular diclofenac provided analgesia superior to either drug alone (20).

In experimental studies, local NSAID application for burn injuries has proven effective in reducing various aspects of the injury response as well as pulmonary complications (21), but the analgesic effect in clinical burn injury is debatable (22). No information is available from local instillation of NSAID in surgical procedures. Combination of systemic NSAID with intraarticular bupivacaine may reduce pain and analgesic requirements (23).

So far, no NSAID has been proven superior regarding efficacy or side effects (12,13) and choice of preparation therefore may depend on other factors, such as duration and site of administration (intravenous, suppositories, oral, cream). Short-lasting (<1 wk) treatment with NSAIDs does not seem to have clinically significant side effects (12,13), except in high-risk patients with hypovolemia, renal failure, active or recent gastroduodenal ulcer, or bleeding disorders (12,13).

The use of other modifiers of the primary hyperalgesic (inflammatory) response has not been evaluated in clinical postoperative pain, as far as leukotriene synthesis inhibitors, bradykinin-, substance-P-, or serotonin-antagonists, and α_2-agonists are concerned. Therefore, no data are available on combination regimens with these drugs together with other peripheral acting analgesics.

In conclusion, treatment with peripheral-acting analgesics may be an important component of multimodal pain therapy in the future, but, because there is a lack of data, no firm recommendations can be given. However, the combined use of NSAID and opioids seems rational and is supported by the available data.

Peripheral Nerve Blocks

The gold standard for peripheral nerve blocks is local anesthetics, and recently there have been efforts to prolong or optimize analgesic efficacy by combining the local anesthetic with opioids or clonidine (24,25). In this respect there is some evidence from experimental isolated nerve studies that clonidine may enhance the effects of lidocaine on C-fiber action potentials (26). However, at present, the results are clinically inconclusive and recommendations can not be given. One study has demonstrated additive analgesic effects by a combination of cryoanalgesia and rectal indomethacin after thoracotomy (27).

Central Neural Blocks with Local Anesthetics, Opioids, and α_2-Agonists

The clinical data showing the additive/synergistic analgesic effects of combining epidural local anesthetics, opioids, and α_2-agonists are in accordance with results from experimental studies.

Experimentally, intrathecal local anesthetics potentiate spinal morphine antinociception (28,29) and together inhibit prolonged poststimulation discharge (wind-up) of the dorsal horn cells (30). The synergism between morphine and lidocaine also exists in visceral nociception models, and may be more profound than the inhibition of somatic nociception (31). The mechanism for the additive/synergistic effects between spinal local anesthetic and opioid effects has not been evaluated clearly (29), although bupivacaine may facilitate morphine-induced antinociception by conformational changes in spinal opioid receptors with decreased binding to μ-receptors but increased binding to δ- and κ-receptors (32). Experimental studies have also shown additive effects between intrathecal opioid and α-adrenergic agonists (33–35). This has been confirmed in more recent studies also demonstrating additive effects between intrathecal morphine combined with norepinephrine, carbacol, or midazolam (36).

Epidural Local Anesthetic-Opioid Combinations

Morphine enhances pain relief and the spread of sensory analgesia during continuous epidural bupivacaine infusion (37). Tables 1 and 2 summarize the available data from double-blind or single-blind studies, matched, or other sufficient comparative studies investigating the analgesic power of continuous epidural local anesthetic with or without opioid or epidural opioid with or without local anesthetic. The interpretation is hindered somewhat by differences in design, but due to the relatively large number of studies, reasonable conclusions and directions for the use and future applications of such mixtures can be made. A variable dose regimen, not always presenting exact infusion rates, has been performed in about half of the available studies (38–44). High-dose bupivacaine-morphine infusions have been used in the studies by Hjortsø et al. (45) and Scott et al. (46), who used doses so large that they can not be recommended for common clinical use. However, these studies are included because they are appropriate for the discussion of potential additive/synergistic effects of combining local anesthetics and opioids. The study by Badner and Komar (43), which is negative for the combination therapy, can not be compared to the other studies, since a lumbar (L1-3) epidural catheter with local anesthetic infusion was used, despite the fact that operations were upper abdominal or thoracic procedures.

To examine whether a combination of local anesthetic and opioid is more effective than either local anesthetic or the opioid alone, studies have been divided into two groups: studies in which the basic analgesic solution was opioid with or without additional local anesthetic, *or* studies in which the basic analgesic solution was local anesthetic with or without additional opioid (Table 2). In all studies in which the basic infusion consisted of bupivacaine, additional opioid improved analgesia (Table 2). On the other hand, the studies using opioid as a basic analgesic solution with or without additional local anesthetic administration do not agree, inasmuch as only three studies showed improved analgesia by the combination (40,42,47), whereas five studies (38,39,41,43,48), could not demonstrate improved analgesic power by the combination versus the opioid infusion alone. In this context, only two studies have assessed pain during rest as well as during cough, mobilization, or exercise (42,47). This is important because in both these studies, the superiority in analgesic power of the combination therapy, versus opioid infusion alone, only became manifest when pain was assessed during cough, mobilization, and exercise, but not during pain at rest (42,47).

Table 1. Summary of Studies Using Epidural Combinations of Local Anesthetics and Opioids for Postoperative Pain Relief

Reference	Type of Surgery	Analgesia regimen	Pre-emptive analgesia	Duration (h)	Pain assessed during			Analgesic efficacy	Side effects
					Rest	Cough	Mobility		
Cullen et al., 1985 (38)[a,b]	Major abdominal	B, 4 mg/h, n = 15 S, n = 15 M, 0.4 mg/h, n + 18	+	72	+			B + M = M > B and S	
Hjortsø et al., 1986 (45)[c]	Major abdominal	B, 0.5% 8 mL/h, n = 10 B + M, 0.5 mg/h, n = 10	+	16	+			B + M > B	
Logas et al., 1987 (39)[a,b]	Thoracic	B, 4 mg/h, n = 10 M, 0.4 mg/h, n = 10 S, n = 10 B + M, n = 11	+	72	+			B + M = M > B and S	1 respiratory depression in B group
Lee et al., 1988 (49)[b]	Hysterectomy	B, 0.125% 15 mL/h, n = 20 Diamorphine (M), 0.5 mg/h, n = 20 B + M	+	21	+			B + M > B and M	Motorblock in B and B + M groups
Scott et al., 1989 (46)[b]	Abdominal	B, 0.5% 8 mL/h, n = 10 B + M, 0.5 mg/h, n = 10	+	16	+			B + M > B	
George et al., 1991 (40)[a,b]	Thoracotomy	Fentanyl, (M), 50 µg/h, n = 11 + B, 10 mg/h, n = 10	+	48	+			B + M > M	1 limb weakness in B group
Badner et al., 1991 (41)[a,b]	Orthopedic	Fentanyl (M), 80 µg/h, n = 14 M + B, 0.1% 8 mg/h	?	48	+			B + M = M	1 respiratory depression and 1 hypotension in B + M groups
Asantila et al., 1991 (48)[d]	Hysterectomy	B, 0.25% 4 mL/h, n = 20 M, 2 mg + 0.2 mg/h, n = 20 B + M, n = 20	+	24	+			B + M = M > B	
Mourisse et al., 1992 (42)[a,e]	Thoracotomy	B, 0.125%, 8 mL/h, n = 10 Sufentanil, (M), 7 µg/h, n = 20 B + M, n = 20	+	72	+		+	B + S = S > B (at rest) B + S > S (exercise)	1 orthostatic hypotension in B and S groups; S groups lowest respiratory rate
Dahl et al., 1992 (47)[b]	Major abdominal	M, 2 mg + 0.2 mg/h, n = 12 M + B, 0.25%, 4 mL/h, n = 12	+	48	+	+	+	M + B > M	
Badner and Komar, 1992 (43)[b,f]	Abdominal/ thoracic	Fentanyl (M), 10 µg/mL, 8 mL/h, n = 15 M + B, 0.1%, 8 mL/h, n = 15	?	24	+			B + M = M	2 Bromage 1 paralysis in B + M groups
George et al., 1992 (44)[a,b]	Major abdominal	B, 0.2%, 8 mL/h, n = 10 Fentanyl (M), 10 µg/mL, 8 mL/h, n = 10 B + M, n = 10	+	24	+			B + M > B and M B = M	2 limb weakness in B group

B = bupivacine; S = saline; M = morphine.
[a] Variable dose rate.
[b] Randomized, double-blind study.
[c] Matched study.
[d] Randomized, single-blind study.
[e] Nonblinded, nonrandomized design.
[f] Interpretation difficult; lumbar epidural for upper abdominal thoracic surgery.

Table 2. Summary of Analgesic Power of Combined Epidural/Opioid Local Anesthetic Regimens

Epidural combination most efficient			
Epidural opioid + bupivacaine versus opioid only		Epidural bupivacaine + opioid versus bupivacaine only	
Yes	No	Yes	No
George et al., 1991 (40)	Cullen et al., 1985 (38)	Cullen et al., 1985 (38)	
Mourisse et al., 1992 (42)*	Logas et al., 1987 (39)	Hjortsø et al., 1986 (45)	
Dahl et al., 1992 (47)*	Badner et al., 1991 (41)	Logas et al., 1987 (39)	
	Asantila et al., 1991 (48)	Lee et al., 1988 (49)	
	Badner and Komar, 1992 (43)	Scott et al., 1989 (46)	
		Asantila, et al., 1991 (48)	
		Mourisse et al., 1992 (42)	
		George et al., 1992 (44)	

* Denotes that pain was also assessed during function.

In summary, these studies suggest that the difference in analgesic power between epidural opioid alone versus epidural opioid plus local anesthetic at low infusion rates, is probably small when pain is assessed at rest, whereas more pronounced and clinically relevant analgesia is achieved with the combination therapy when pain is assessed during function (which, in fact, is the aim of postoperative pain therapy).

Side Effects

Regarding side effects of the different low-dose regimens, the relatively small size of these studies does not allow conclusions as to the clinical relevance and recommendations. In most studies, respiratory depression or orthostatic hypotension has not occurred, although the latter has not been studied sufficiently with well-defined criteria. However, in the moderate size infusion rate study by Lee et al. (49) the bupivacaine group had an unacceptably high incidence of motor block. Limb weakness also was found in 2 of 20 patients in the bupivacaine infusion regimens by George et al. (44). Also, two cases of muscle paralysis were found by Badner and Komar (43) in the bupivacaine infusion group of 15 patients receiving lumbar epidural analgesia, despite upper abdominal and thoracic procedures. One case of respiratory depression was found in the bupivacaine only group by Logas et al. (39) and in the bupivacaine-fentanyl group by Badner et al. (41) and in the sufentanil group by Mourisse et al. (42).

In the only available study of the risk of adverse cardiovascular responses to mobilization and walking with or without a low-dose epidural bupivacaine-morphine combination (10 mg/0.2 mg/h), no risk was found by *thoracic* epidural analgesia in patients undergoing cholecystectomy (50). Obviously, similar well-defined studies on cardiovascular function during low-dose *lumbar* epidural infusions are needed to allow clinical recommendations of optimal dose regimens.

With regard to bladder function, differences in design, as well as indications for a postoperative urinary bladder catheter and time for removal, preclude any conclusions as to the most optimal combination.

Inasmuch as the available data seem to indicate that the combined epidural local anesthetic-opioid therapy is most efficient on pain during function, four questions need to be answered: 1) Is continuous or intermittent therapy preferable? 2) Which local anesthetic and opioid should be used? 3) Where should the epidural catheter for the combined local anesthetic-opioid administration be inserted? 4) What are the optimal dosage regimens?

Intermittent or Continuous Infusion

With regard to intermittent versus continuous infusion therapy, there is probably not much difference in efficacy during opioid therapy, at least not with the longer-acting drugs such as morphine and diamorphine (51,52), although similar studies are not available with the shorter-acting lipophilic drugs. Local anesthetics need to be administered by an infusion (53), because intermittent injections will increase the risk of adverse effects, such as muscle paralysis, orthostatic hypotension, and bladder dysfunction, although good comparative studies are not available.

Choice of Opioid

Lipophilic opioids may have a segmental analgesic effect, thereby hopefully limiting side effects (e.g., respiratory depression, nausea, vomiting). However, this conclusion has not been proven by any large scale study. In one obstetrical pain study, fentanyl led to a reduced incidence of nausea and pruritus compared with morphine when combined with bupivacaine (54). An unblinded and variable dose study in major orthopedic surgery found more nausea and pruritus and higher $Paco_2$ values after morphine (about 0.4 mg/h), but less sedation compared with fentanyl (about 50 μg/h) (55). Another variable dose study showed comparable analgesia, but less pruritus after hydromorphone, compared with morphine (56).

Morphine (57–59) and probably diamorphine (60,61) have more analgesic efficacy when used epidurally compared with systemic administration. When using the lipophilic opioids, a comparison of epidural versus intravenous fentanyl (62–69), sufentanil (70), and alfentanil (71), have almost uniformly shown no significant differences in analgesic power or side effects between the two routes of administration. The *choice of opioid* for the epidural mixtures, therefore, may depend on other factors, such as price or availability, and in many places morphine may be the optimal opioid. The risk of late respiratory depression may be higher after morphine, but based upon the experience with the recent low-dose, continuous infusion regimens (about 0.2 mg of morphine or about 50–80 μg/h of fentanyl), the large study from Seattle (72) and the nationwide observations from Sweden (73) after higher single or multiple dose administrations, this risk must be extremely low and is probably even lower than after intermittent systemic opioid administration with conventional doses. Finally, late respiratory depression after fentanyl also has been reported (74), and there is no indication of a reduced risk with long-term use of sufentanil or alfentanil.

The potential use of *mixtures of opioids* to enhance analgesia has not been evaluated, although preliminary observations may suggest a more rapid onset and prolonged duration by combining epidural morphine and fentanyl or epidural morphine and sufentanil (75,76).

Choice of Local Anesthetic

Although few studies are available, bupivacaine is most suitable due to its long duration and absent neuro- and cardiotoxicity with low-dose infusion rates (53). Furthermore, most experience comes from this drug. Therefore, bupivacaine must be considered the drug of choice for epidural postoperative combination therapy, unless new local anesthetics will be available with a more favorable sensory/motor block profile.

Site of Injection

Insertion of the epidural catheter should be at the middermatomal level of the incision when local anesthetics are used (53). This is in contrast to the use of epidural opioids, in studies in which morphine (77,78) or fentanyl (69,79) have not demonstrated significant differences between thoracic or lumbar application.

Choice of Dosage

Definitive recommendations for dosage can not be given before more information is available from large scale studies comparing analgesic efficacy and risk of side effects, especially the risk of orthostatic hypotension during early postoperative mobilization and bladder dysfunction. Also, such studies should evaluate the potential reduction in dosage when combined with an appropriate NSAID or other analgesics.

So far, during upper abdominal or thoracic procedures, a combination of bupivacaine (approximately 10 mg/h) and morphine (about 0.2 mg/h with a loading dose of 1–2 mg of morphine, dependent on age), seems to be most appropriate. This regimen may not have orthostatic hypotensive effects when used as *thoracic* epidural analgesia (50). During *lumbar* epidural analgesia, less local anesthetic, probably in the range of 2.5–5 mg/h, has to be used due to the risk of motor block and orthostatic hypotension, although sufficient data on the risk/benefit ratio are not available. The amount of opioids may be the same as during upper abdominal and thoracic procedures, i.e., morphine 0.2 mg/h or fentanyl approximately 50–80 μg/h.

Epidural α_2-Agonists and Mixtures

There is considerable experimental evidence that intrathecal or epidural α_2-agonists have an analgesic effect (33–35) and several single-dose clinical studies have documented postoperative analgesic efficacy when used alone or an enhanced effect when used in combinations with local anesthetics or opioids (80–83). When used epidurally, the analgesic effect of clonidine may be due not only to a segmental spinal effect, but also to absorption and a systemic effect (81).

For severe pain, combinations of clonidine with other analgesics (i.e., local anesthetics and opioids) may be appropriate to increase analgesic power and reduce side effects. This may be clinically important, because clonidine has a different side-effect profile compared with opioids. Thus, hypotension and sedation and the lack of respiratory side effects are the most relevant. So far, only three double-blind randomized studies are available with *continuous* infusion of clonidine, either as a combination of clonidine (19 μg/h) and morphine versus morphine alone (84), or comparing clonidine 25 μg/h or 50 μg/h versus low-dose morphine or combined morphine-clonidine (85), or comparing a low-dose bupivacaine-morphine regimen with or without clonidine (19 μg/h) (86). The results of these studies are concordant in that the combination of clonidine and morphine improved analgesia compared with morphine (84,85) or compared with low-dose clonidine alone (85) and also when added to a low-dose epidural bupivacaine-morphine regimen (86). However, hypotension was observed in all three studies.

In conclusion, the addition of clonidine to epidural combination regimens will increase analgesic power, but the infusion rates studied so far (19–25 μg/h) have resulted in hypotension. Although systematic dose-response studies on the risk of orthostatic hypotension

are not available, these findings limit the recommendation for continuous postoperative epidural clonidine therapy. Nevertheless, the positive analgesic results call for further combination studies using a lower dose rate of clonidine or other α_2-agonists.

The use of droperidrol, a dopamine-receptor antagonist with weak α_1- and α_2-agonist properties, did not improve pain relief after hip surgery when combined with morphine, but resulted in fewer side effects (87).

Combinations of Peripheral and Central Analgesic Treatment or Other Mixtures

As previously mentioned, the combination of peripheral-acting analgesics (i.e., NSAID and others) with low-dose epidural regimens seems rational in more severe states of pain to improve analgesia and reduce side effects. However, only two such double-blind studies are available. These are not sufficient to demonstrate additional analgesic power via the addition of piroxicam to an otherwise effective low-dose epidural bupivacaine-morphine regimen after abdominal and thoracic surgery (18,19). This area definitely requires further exploration with other NSAIDs or other peripheral analgesics during different procedures, especially soft tissue trauma surgery, where NSAIDs may be more efficient.

In an approach combining peripherally acting analgesics (NSAID) together with epidural bupivacaine-morphine, the additional effect of a preoperative high-dose glucocorticoid was studied to modify various humoral mediators including pain mediators (arachidonic cascade metabolites, cytokines) (88,89). In both of these small scale studies, a very efficient and especially prolonged pain relief was observed (88,89), and were more efficient than with the epidural combination therapy and NSAID alone (88). These preliminary observations obviously call for further studies regarding the efficacy, as well as the potential side effects, of additional glucocorticoid therapy.

Conclusions and Future Directions

From the available data on the postoperative use of multimodal pain therapy or balanced analgesia, this strategy seems advantageous, inasmuch as analgesic power may be enhanced. However, the expected gain by reducing the risk of side effects compared with more intensive single modality treatment, needs to be evaluated in large scale studies. Also, the optimal combination therapy needs to be evaluated regarding composition and duration for the various surgical procedures. However, at present there is no doubt that during major surgery, continuous epidural, low-dose combination regimens with local anesthetic and opioid are the most effective, and provide an apparent low risk of complications. Again, the benefits obtained from analgesia and, thereby, the possibility for early mobilization hastening of convalescence and reduction in hospital stay, has to be weighed against the potential risks and the cost of surveillance.

Furthermore, the use of multimodal pain therapy in conjunction with effective *preemptive analgesia* (i.e., analgesia given before the painful stimulus) needs to be studied, because preliminary uncontrolled observations have been positive (90). Thus, the use of preemptive analgesia may improve, at least theoretically, the analgesic power of subsequent balanced analgesia (91), although a continuous postoperative treatment may be more important than a short-lasting preemptive analgesia alone (92).

Finally, the use of *patient-controlled multimodal therapy* has to be evaluated, inasmuch as most studies have used rather fixed dosage regimens, which may be suboptimal due to the well-documented, pronounced interpatient variability in analgesic needs after surgery.

In conclusion, the data on multimodal, or balanced, analgesia is relatively scarce compared to studies on the single modality treatment of postoperative pain. Future postoperative pain studies should include such regimens rather than to simply continue investigations of single modality treatment, although single modality treatment studies are obviously useful in the evaluation of new drugs and techniques. The approach that combines the consideration of peripheral and central treatment of pain, possibly in combination with preemptive analgesia, may contribute eventually to a postoperative course without pain, and one that provides for very early mobilization and restoration of function with subsequent reduction in postoperative morbidity and hospital stay.

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