Adjuvant analgesics for spine surgery

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This review has been accepted as a thesis together with four previously published papers by University of Copenhagen on May 5th 2016 and defended on August 31st 2016.

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Dan Med J 2018;65(3)B5468.

The 4 original papers included in the thesis:

1. Preoperative dexamethasone reduces acute but not sustained pain after lumbar disk surgery: a randomized, blinded, placebo-controlled trial. Nielsen RV, Siegel H, Fomsgaard JS, Andersen JD, Martusevicius R, Mathiesen O, Dahl JB. Pain 2015;156:2538-44.
2. The effect of preoperative dexamethasone on pain 1 year after lumbar disc surgery: A follow-up study. Nielsen RV, Fomsgaard JS, Mathiesen O, Dahl JB. BMC Anesthesiol 2016;16;16:112.
3. The effect of chlorzoxazone on acute pain after spine surgery. A randomized, blinded trial. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Mathiesen O, Dahl JB. Acta Anaesthesiol Scand 2016;60:1152-60.
4. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: A randomized, blinded trial. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB, Mathiesen O. Pain 2017;158:463-470.

INTRODUCTION

Increasing evidence indicate that pain is insufficiently treated following surgical procedures (1). It is essential that pain treatment is effective with a minimum of side effects in order to promote rehabilitation and reduce postoperative morbidity (2, 3).

Serious adverse events such as prolonged hospital stay, delayed functional recovery; higher re-admission rates and increased healthcare resources are associated with insufficient perioperative pain management (4-6). Further, there is evidence that reducing acute postoperative pain may reduce the development of persistent postoperative pain (7, 8).

The frequency of spine surgery has increased over the last decade and in Denmark more than 6,000 spine surgeries are performed annually (9). Spine surgery can be associated with severe postoperative pain that can have a negative effect on postoperative recovery (10). In a review of 179 surgical procedures, lumbar fusion and large spinal reconstruction procedures represented three of the top six surgeries with highest pain scores on the first postoperative day (11). Spine surgery includes a high risk of persistent postsurgical pain, with a frequency ranging from 5 % to 75 % (12, 13).

Multimodal analgesia is an important strategy in reducing postoperative pain (3). Combinations of different groups of analgesics with different mechanisms of action may have an additive analgesic effect with fewer side effects compared to using a single drug (14). However, research on multimodal analgesia has yet to disclose a consistent level of success. There is a pronounced lack of documentation for the effects and side effects of these multimodal analgesic regimes (15, 16). This may partly be due to large variations in analgesic doses, combination of drugs and their administration and type of surgery (16).

We considered spine surgery to pose a group of well-defined surgical procedures with moderate to severe pain levels. Hence, we used this well-defined surgical model to investigate the efficacy of 3 different, potential adjuvant analgesics with the aim of improving the multimodal approach in pain management.

BACKGROUND

Multimodal analgesia

Multimodal analgesia is a strategy that utilizes a combination of different analgesic modalities to achieve better postoperative pain management and a subsequent reduction in adverse effects. The hypothesis is that a combination of different groups of anal-

gesic drugs may have an additive analgesic effect with fewer adverse effects compared to using single drug therapy (15, 17, 18). Hence, this strategy could be favourable in the management of pain after spine surgery, being a procedure that involves dissection of many tissues and consequently pain arises from muscles, bone tissue, intervertebral disks, ligaments, nerves, facet joint capsules and fascia (10, 19).
This multimodal approach is recommended to reduce postoperative pain, however there is a lack of evidence regarding optimal postoperative protocols for this strategy in general as well as for spine surgery specifically (15, 17, 18).

Analgesics commonly used in multimodal regimes include combinations of opioids, paracetamol, NSAIDs, selective COX-2 antagonists, glucocorticoids, gabapentin, pregabalin, ketamine and local- and regional anaesthetics (17, 20). A large number of trials document the analgesic effect of paracetamol, non-selective NSAIDs and selective COX-2 antagonists when administered as monotherapy (21-23). Further, paracetamol and NSAIDs may represent an effective basic analgesic regimen when combined, but the scientific evidence is limited (14, 15, 24). The effect of gabapentin and glucocorticoids in multimodal regimes is not well documented. Meta-analyses are based on both mono-therapeutic and polytherapeutic trials, making the analysis of the additive or synergistic effects of combining the drugs difficult (25-27). Evidence regarding the ability of ketamine to provide a significant reduction in postoperative pain or opioid use is conflicting (18). Reporting of adverse events in combination therapy studies is generally sparse and often the studies do not reach the statistical power to sufficiently detect adverse events (28). Further, observation time is often limited to the acute postoperative period and thus evidence of long term effects and adverse events is lacking (28).

The possible combinations of non-opioid analgesics and techniques are many. However, current knowledge is based on studies exploring many different drug combinations and doses in relatively small trials with low statistical power, and heterogeneity in outcome measures.

Dexamethasone
Glucocorticoids are a class of steroid hormones that bind to the glucocorticoid receptors. The effect on postoperative pain is possibly due to an inhibition of the inflammatory response in the area of injury (29). Further, a reduction in central sensitization has been hypothesized due to a protracted effect seen in a trial demonstrating sustained postoperative opioid sparing and pain relief continuing for 3 days after one single dose of glucocorticoids (30).

Dexamethasone is a synthetic potent glucocorticoid with hardly any mineralocorticoid effect. When administered intravenously the time of onset is one hour, the plasma half-life is 4.5 – 6 hours and biologic half-life 36 – 54 hours.

Many trials have explored glucocorticoids as possible analgesic adjuvants in the treatment of acute postoperative pain (26, 27). Two systematic reviews (including many of the same original trials) have analyzed the effects of perioperative administration of dexamethasone on acute postoperative pain (26, 27). The first review indicated that dexamethasone at doses above 0.1 mg/kg reduces pain, and provides an (non-specified) opioid-sparing effect after surgery (27). The other review and meta-analysis, demonstrated that dexamethasone in doses of 1.25 - 20 mg resulted in lower pain scores, and a small reduction in opioid consumption the first 24 hours after surgery (mean difference 2.33 mg morphine (95% confidence interval 0.26, 4.39)) (26). A few trials of high-dose glucocorticoid (125 mg methylprednisolone) have indicated substantial analgesic effects after orthopedic surgery (31, 32). Regarding adverse events the reporting is sparse but several reviews and meta-analyses on both minor and major surgery have found no significant differences in wound infection and wound healing (26, 27, 33). However findings based on several trials still indicate potential increased risk of elevated blood glucose levels, gastrointestinal bleeding and myocardial injury (28, 34, 35).

Chlorzoxazone
Chlorzoxazone is a muscle relaxant used to treat musculoskeletal pain, and as an analgesic adjunct in postoperative pain treatment (18). Chlorzoxazone was first introduced in 1958, and is a centrally acting muscle relaxant that functions mainly by inhibiting multisynaptic reflex arcs implicated in producing and maintaining skeletal muscle spasm at the level of the spinal cord and subcortical areas of the brain (36, 37). The onset of action is within 1 hour and plasma half-life is 1-2 hours. Length of action is 3-5 hours (37, 38). The specific mechanism of action is not clear, but is hypothesized to be associated to sedative effects due to the benzodiazepine derivative structure of chlorzoxazone (38, 39).

A Cochrane review from 2003 exploring the effect of muscle relaxants in unspecified low back pain concludes that muscle relaxants are more effective as short term treatment of acute back pain than placebo, but side effects could limit their use (39). However, data describing their analgesic action is lacking, and especially regarding an independent analgesic effect unrelated to the sedative properties of muscle relaxants. Therefor chlorzoxazone is currently not recommended in the literature (36, 39). Chlorzoxazone is used as an adjuvant analgesic for acute postoperative pain after various surgical procedures, including spine surgery, primarily administered to the subgroup of patients with severe pain, if other analgesic options have failed (40). However, there are no published studies examining the effect of chlorzoxazone on acute postoperative pain after spine surgery (18).

Ketamine
Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism of action is blockage of the NMDA receptors in the central and peripheral nervous system. Further, animal studies indicate that ketamine also holds mechanisms of action including reduction of central sensitization and reducing postoperative opioid tolerance by antagonizing the

NMDA receptors (41, 42). A low dose of ketamine possibly modulates the opioid receptors (43, 44).
Previous trials have demonstrated a reduction in pain up to 48 hours postoperatively, a reduction in the cumulated opioid consumption of up to a 50% and prolonged time tothe need for rescue analgesics when sub-anaesthetic doses of ketamine are administered intravenously during surgery (44-48). Timing of administration (pre- or post-incision) and size of dose does not seem to influence the effect (48). One trial on spine surgery demonstrated that opioid dependent patients receiving intraoperative ketamine used significantly less opioids the first 48 hours postoperatively (ketamine: 195 (111) mg morphine-equivalents; placebo: 309 (341) mg morphine- equivalents (mean (SD)), and experienced less pain than the placebo group (43). Theoretically intraoperative low dose ketamine can be indicated in this patient population to reduce hyperalgesia and increase opioid sensitivity (43, 49).

Besides the opioid sparing effects of ketamine it can possibly reduce the development of persistent postoperative pain by blocking the NMDA-receptors and reducing wind-up and central sensitization (44, 50). A recent review and meta-analysis investigated ketamine's role in preventing persistent postoperative pain (51). In their analysis only one of nine pooled estimates of persistent pain demonstrated marginally significant pain reduction (51). The effect of ketamine persistent pain is still relatively unexplored (47, 51).
Regarding adverse effects, hallucinations and nightmares are a concern, but in patients undergoing general anaesthesia along with sub-anaesthetic doses of S-ketamine as an adjuvant, the risk of side effects seems to be minimal (44, 45).

HYPOTHESIS AND AIM

The overall aim of this thesis was to investigate the efficacy of 3 potential adjuvant analgesics on spine surgery, aspiring to improve the multimodal approach in pain management.

Study I and II: We hypothesized that preoperative IV dexamethasone 16 mg would reduce acute postoperative pain and opioid consumption after lumbar disk surgery and that dexamethasone would reduce persistent pain 3- and 12 months postoperatively.

Study III: We hypothesized that 500 mg of oral chlorzoxazone would reduce acute postoperative pain and opioid consumption in patients with moderate to severe pain after spine surgery.

Study IV: We hypothesized that intraoperative ketamine would reduce postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency and that ketamine would reduce persistent pain 6 months postoperatively.

BASIC METHODOLOGY

Study I, III and IV were single-centre prospective, randomized, blinded trials approved by the Regional Research Ethics Committee and the Danish Data Protection Agency and registered at clinicaltrials.gov. All trials were conducted at the Department of Neuroanaesthesiology, Rigshospitalet - Glostrup, Copenhagen University Hospital and were monitored by the Copenhagen University Hospital Good Clinical Practice Unit. The studies fulfilled the guidelines for Good Clinical Practice and the Helsinki Declarations. Study II was a prospective 1-year follow-up trial on the patients from study I. All patients gave written informed consent before participating in the trials.

Table 1. Inclusion- and exclusion criteria, study I, III and IV.

INCLUSION	**Study I**	**Study III**	**Study IV**
Age	18 - 85	18 - 85	18 - 85
BMI (kg/m^2)	18 - 40	18 - 40	18 - 40
ASA class	I-III	I-III	I-III
Procedure	Lumbar disk surgery	All spine surgery	Lumbar fusion
Anaesthesia	General anaesthesia	Not standardized	General anaesthesia
Trial period	48 hours	4 hours	24 hours
Basic analgesia	PCM,NSAID,PCA morphine	PCA morphine	PCM,PCA morphine
Chronic pain			Pain >3 months
Opioids*			Daily use >6 weeks
EXCLUSION			
Opioids	Daily use not allowed**	Daily use not allowed**	
Spine surgery	Previous lumbar spine surgery not allowed		

*Opioids = morphine, oxycodone, methadone, fentanyl, tramadol, ketobemidone. ** Tramadol allowed.

Additional exclusion criteria for all trials were inability to cooperate, inability to speak or understand Danish, participation in other drug trials, daily use of methadone, daily use of the study-drug, pregnancy, allergy to drugs applied in the trial, and alcohol or drug abuse. In study IV further exclusion criteria were previous or current psychotic episodes, uncontrolled hypertension and increased intraocular pressure.

Basic analgesic regime

Current protocols for postoperative pain management contain basic analgesics including paracetamol and NSAIDs. Further, PCA with opioids is a frequently applied method for rescue analgesia. Therefor we decided to include these analgesics in our study designs (52). In study I all patients received 1000 mg oral paracetamol and 400 mg oral ibuprofen preoperatively and starting two hours postoperatively every 6 hours during the 48 h trial period. In study IV patients continued with their usual daily dose of opioids and received 1000 mg oral paracetamol preoperatively and starting two hours postoperatively every 6 hours during the 24 h trial period.

In study I, III and IV all patients received IV PCA with morphine bolus 2.5 mg and no background infusion. In study I and III, lock-out time was 10 minutes. In study IV lock-out time was reduced to 5 minutes because a higher analgesic need was expected. In study I the PCA was discontinued after 24 hours and patients were discharged with paracetamol and ibuprofen as above and capsules of morphine 5 mg on request for the next 24-48 hours.

Outcome measures

Pain was measured on a visual analogue scale (0–100 mm; 0, no pain; 100, worst imaginable pain). All investigators and relevant staff were experienced using this measurement tool. Pain was measured at rest lying in bed and during movement, standardized as the movement from recumbent position to sitting bedside. Patients were instructed in this movement by the department's physiotherapists. Total morphine consumption was read from the PCA by the primary investigator when the PCA was discontinued. The patients evaluated nausea, sedation and dizziness on a verbal rating scale: none, light, moderate, and severe (0 – 3). Numbers of vomiting episodes with a volume greater than 10 ml (assessed by the nurse) were registered. The need for antiemetics was recorded. Episodes of hallucinations or nightmares were recorded in study IV.

Sample size calculations

Study I: Data gathered in our own department showed that mean VAS pain scores during mobilization 2-24 h postoperatively were 45 mm, SD 25 (40). We considered a reduction of 12 mm to be clinically relevant. With a type 1 error (α) of 5 % and a power (1 - β) of 80 %, sample size calculations showed that 70 patients in each group were needed to demonstrate this difference in pain. Taking dropouts and uncertainty about our calculated SD into account, we included 160 subjects.

Study III: There were no published studies testing chlorzoxazone on acute postoperative pain. Therefor we considered a reduction in pain intensity of 12 mm during mobilization 2 hours after intervention to be clinically relevant. To identify this reduction in pain, calculations settled that we needed a sample size of 98 patients with a type 1 error (α) of 5 %, and a power (1 - β) of 80 %. We included 110 patients to compensate for dropouts and inaccuracy of the standard deviation.

Study IV: Data from the same trial referred to in study I, showed that spinal fusion patients have an mean morphine consumption 0-24 h postoperatively of 36 mg IV, SD 24 (40). With a type 1 error (α) of 5 % and a power (1 - β) of 80 %, sample size calculations showed that 64 patients in each group were required to detect a 30 % reduction in morphine consumption. Taking dropouts and uncertainty about our calculated SD into account, we included 150 subjects.

Statistical analyses

Variables were tested for normal distribution with the Kolmogorov-Smirnov test and visual inspection of histograms. Data that followed normal distribution were compared using the independent samples t test. The Mann-Whitney *U*-test was used for data that were not normally distributed. Categorical data were analyzed using the x^2 test or Fisher's exact test if any cells had expected counts less than five. Data are presented as mean (SD) or (95% CI) with mean difference (95% CI), median (percentiles) or frequencies (95% CI), as appropriate. AUC pain data are presented as weighted average AUC (in mm) for the period calculated according to the method described by Altman (53). For comparisons of nausea, sedation and dizziness scores, we calculated the arithmetic mean scores by attributing numerical values to the scores from each patient (0 - 3).

The nature of the hypothesis testing was 2-tailed. P-values of less than 0.05 were considered statistically significant. Secondary outcome measures were Bonferroni corrected except the results in study II and the 6 months follow-up data in study IV that were not corrected for mass significance.

METHODS AND RESULTS

Study I

Methods

In this study patients were randomized to 16 mg dexamethasone IV or placebo prior to undergoing first time lumbar disk surgery on 1-2 levels. The study medication was administered immediately after induction of standardized general anaesthesia. Pain, sedation, nausea and vomiting were evaluated at 2, 4, 8, 12, 24 and 48 h postoperatively. Cumulated morphine consumption was registered from 0-24 h and 24-48 h postoperatively. Quality of sleep was assessed 24 h postoperatively. Patients were followed up 3 months postoperatively by written questionnaire. Outcomes for the 3-month follow-up included back and leg pain (VAS 0-100 mm), use of analgesics, postoperative complications including wound infections, walking distance, duration of sick leave, working capability and contentment with the results of the operation.

Results

We included and randomized 160 patients. Seven patients were excluded, leaving 153 patients in the final analysis.

The primary outcome pain during mobilization (weighted average, AUC 2-24 h) was significantly reduced in the dexamethasone group compared to the placebo group: 33 (22) *vs* 43 (18) mm with a mean difference of 10 mm (95% CI 3 to 16), P=0.005 (Fig. 1). For pain at rest (weighted average AUC 2-24 h) there was no signifi-

cant difference between groups: 23 (17) *vs* 26 (15) mm in the dexamethasone and placebo groups, respectively, with a mean difference of 3 mm (95% CI -2 to 8), P=0.27. No significant differences on pain 48 h postoperatively were detected.

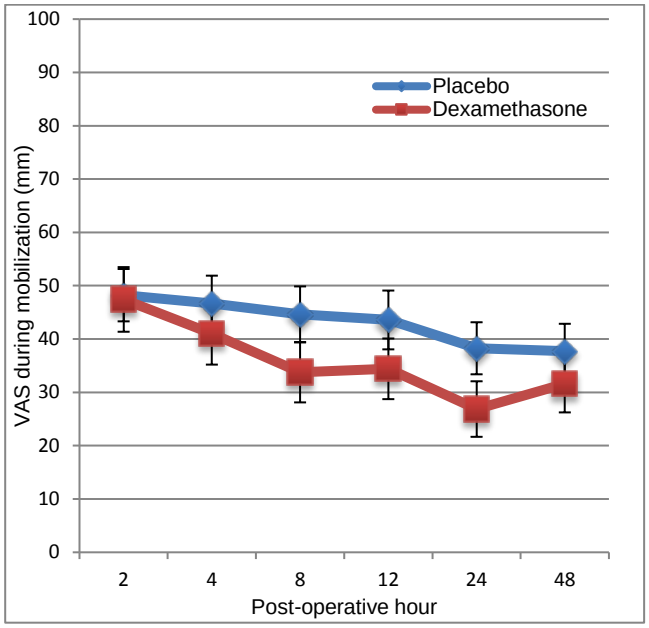

Figure 1. Pain (VAS) during mobilization (weighted average AUC 2-24 h). Data are mean, error bars are 95% CI.

The total number of vomiting episodes 0-24 h was significantly reduced in the dexamethasone group (17 episodes) *vs* placebo (51 episodes) (P=0.036). However, for nausea, sedation and ondansetron consumption there were no significant differences between groups. Further, there was no significant difference between groups in quality of sleep assessed 24 h postoperatively. Three months postoperatively, back pain in the dexamethasone group was 19 (95% CI 13 – 25) *vs* 22 (95% CI 15 – 29) mm in the placebo group (P=0.75). Leg pain was 27 (95% CI 20 – 33) *vs* 23 (95% CI 15 – 30) mm in the dexamethasone and the placebo groups, respectively (P=0.50). There were no significant differences regarding use of analgesics, walking distance, duration of sick leave, working capability and contentment with the results of the operation. However 6.5 % (95% CI 2 – 15) in the dexamethasone group versus placebo 0 % had an antibiotically treated wound infection (P=0.13). Sixteen percent (95% CI 7 – 26) versus 8 % (95% CI 0 – 17) reported new weakness/paralysis of the legs in the dexamethasone and placebo groups, respectively 3 months postoperatively (P=0.20).

Study II

Methods

This was a prospective 1-year follow up study on study I. The 1-year follow-up was performed by written questionnaire. If patients had not returned the questionnaire within three weeks, they received one written reminder. The questionnaire consisted of demographic data, back and leg pain (VAS 0-100 mm), duration of sick leave, working capability and contentment with the results of the operation. Further it contained the following questionnaires: Short form 36 survey (SF-36), EuroQol 5D (EQ-5D) and OSWESTRY Low Back Pain Questionnaire.

Results

Seventy-seven patients in the dexamethasone group and 76 patients in the placebo group received a follow-up questionnaire. In the dexamethasone group 55 patients (71 %) replied, and in the placebo group 44 patients replied (58 %).

Leg VAS pain levels was significantly lower in the placebo group compared to the dexamethasone group: 17 (95 % CI 10 - 26) *vs* 26 (95 % CI 19 - 33) mm, respectively (mean difference 9 mm (95% CI -1 to 0), (P = 0.03) (Fig. 2). For VAS back pain levels at one year postoperatively, there was no significant difference between groups: 22 (95 % CI 16 - 28) *vs* 20 (95 % CI 14 - 28) mm in the dexamethasone and placebo groups, respectively (mean difference 2 mm (95% CI -1 to 0), P = 0.47 (Fig. 2)).

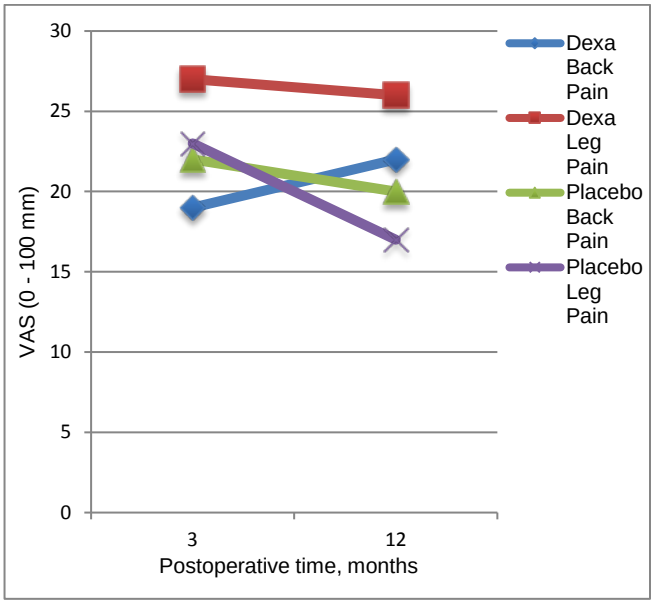

Figure 2. Postoperative back- and leg pain (VAS). Data are mean.

When asked how patients evaluated their leg pain today compared to preoperatively, the placebo group reported a significantly higher degree of improvement of their leg pain, compared to the dexamethasone group: 1 (0 – 5) *vs* 2 (0 – 5), respectively, (P = 0.04). Daily use of analgesics was not different between groups. Satisfaction with the surgical result was significantly lower in the dexamethasone group compared to the placebo group. Patients in the dexamethasone group reported significantly higher pain levels in EQ-5D- and Oswestry questionnaires. No significant differences in SF-36.

Study III

Methods

All patients who had undergone spine surgery were approached for inclusion in the PACU at any time point after their surgery, if they had pain scores of >50 mm on the VAS scale during mobiliza-

tion, (standardized as the movement from recumbent position to sitting bedside) and had not received any analgesics during the last 60 minutes. Immediately after inclusion patients were randomized to 500 mg oral chlorzoxazone or placebo.
The primary outcome was pain during mobilization 2 h after taking the study medication (VAS 0-100 mm). Secondary outcomes were pain at rest, pain during mobilization measured as area under the curve (AUC) 1 – 4 h, total morphine use (0 – 4 h), adverse effects associated with morphine and chlorzoxazone (nausea, vomiting, dizziness, sedation) and postoperative use of antiemetics.

Results

In this study 110 patients were enrolled and randomly assigned to intervention or placebo. No patients were excluded and final analyses contained 54 patients in the chlorzoxazone group and 56 patients in the placebo group.
For the primary endpoint, pain during mobilization 2 h after the intervention, there was no significant difference between groups: 51 (21) *vs.* 54 (25) mm in the chlorzoxazone and placebo groups, respectively, mean difference of 3 mm (95% CI -8 to 10), P = 0.59 (Fig 3).
For pain during mobilization (weighted average AUC 1 - 4 h) we found no significant difference between groups: 54 (21) *vs.* 54 (22) mm in the chlorzoxazone and placebo groups, respectively, mean difference of 0.9 mm (95% CI -7 to 9), P = 0.84 (Fig 3).

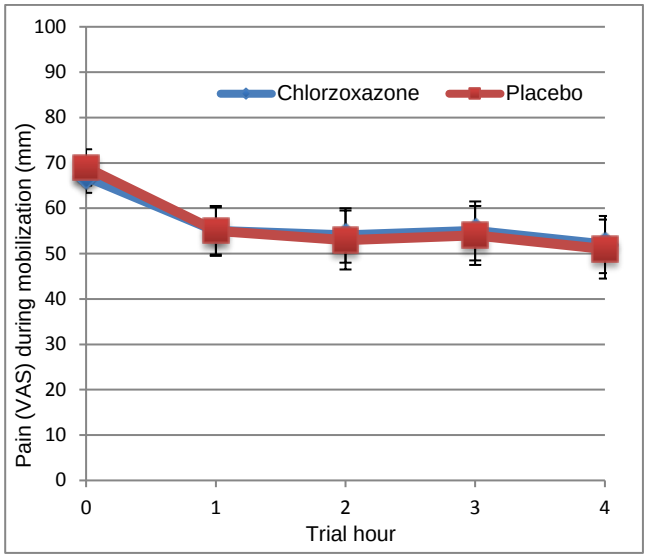

Figure 3. Pain (VAS) during mobilization. Data are mean; error bars are 95% CI.

For pain at rest (weighted average AUC 1 - 4 h) there was no significant difference between groups: 43 (18) *vs.* 41 (19) mm in the chlorzoxazone and placebo groups, respectively, mean difference of 1.2 mm (95% CI -6 to 8), P = 0.74. We found no significant difference in total use of morphine 0-4 h after trial medication: Median 10 (7 - 21) *vs.* 13 (5 - 19) mg IV PCA-morphine in the chlorzoxazone and placebo groups, respectively, median difference of 3 mg (95% CI -3 to 6), P = 0.82. Further, adverse event rates were very similar between groups with no significant differences.

Study IV

Methods

Chronic pain patients with a daily opioid consumption undergoing lumbar fusion surgery were randomly assigned to one of two groups: S-Ketamine (25 mg/ml) bolus 0.5 mg/kg immediately after induction of anaesthesia followed by infusion S-Ketamine 0.25 mg/kg/h or placebo. Preoperatively all patients filled out written questionnaires screening for chronic pain (Brief Pain Inventory), pain-catastrophizing (Pain Catastrophizing Scale), and anxiety and depression (Hospital Anxiety and Depression Score). The primary outcome, cumulated PCA morphine consumption, was registered from 0-24 h postoperatively. Secondary outcomes, pain and adverse effects (sedation, nausea, vomiting and use of antiemetics), were evaluated at 2, 6, 12, 18 and 24 h postoperatively. Episodes of hallucinations or nightmares were recorded 24 h postoperatively.
The 6-month follow-up was performed by a written questionnaire. If patients had not returned the questionnaire after three weeks, they received one written reminder. The questionnaire consisted of demographic data, back and leg pain (VAS 0-100 mm), duration of sick leave, working capability and contentment with the results of the operation. Further it contained the following questionnaires: Short form 36 survey (SF-36), EuroQol 5D (EQ-5D), OSWESTRY Low Back Pain Questionnaire and The Douleur Neuropathique 4.

Results

The primary outcome, total PCA morphine consumption was significantly reduced in the ketamine compared to the placebo group: 79 (47) *vs* 121 (53) mg IV with a mean difference of 42 mg (95% CI -59 to -25), P < 0.001.

Pain during mobilization (weighted average, AUC 2-24 h) was similar in the ketamine and placebo groups: 63 (21) *vs* 64 (18) mm respectively, with a mean difference of 1 mm (95% CI -8 to 5), P=0.627. Likewise for pain at rest (weighted average AUC 2-24 h) there was no significant difference between groups: 46 (19) *vs* 48 (20) mm in the ketamine and placebo groups, respectively, with a mean difference of 2 mm (95% CI -8 to 5), P=0.615. Sedation was generally lower in the ketamine group, and significantly reduced 6 h and 24 h postoperatively. There were no significant differences between groups regarding hallucinations or nightmares 0-24 h postoperatively. Further there were no significant differences in nausea scores, vomiting or ondansetron consumption between groups.

Six months postoperatively back pain levels (VAS) were lower in the ketamine group compared to the placebo group: median 30 (11 - 58) *vs.* 54 (22 - 70) mm, respectively, P=0.041 (Table 2). Regarding daily use of analgesics, consumption of paracetamol was significantly reduced in the ketamine group: 1000 (0 – 3000) mg vs. 3000 (0 – 4000) mg respectively, P = 0.023 (Table 2). Opioid, NSAID and gabapentin consumptions, were lower in the ketamine group but without significant difference. Overall scores

in the questionnaires were better in the ketamine group however only significant for the OSWESTRY Low Back Pain index score, reporting moderate disability in the ketamine group compared to severe disability in the placebo group, P = 0.006.

Table 2
Follow-up 6 months postoperatively.

		Ketamine	Placebo	*P*-value
Patient characteristics				
Number of patients, n		43	52	
Response rate, %		58	71	
Time from operation to follow up, days		183 (175 – 192)	183 (173 – 200)	0.99
Height, cm		173 (8)	170 (8)	0.21
Weight, kg		79 (13)	75 (14)	0.15
Gender female/male		26 / 17	34 / 18	0.44
Outcome				
VAS back pain, 0-100 mm		30 (11 – 58)	54 (22 – 70)	0.041
VAS leg pain, 0-100 mm		30 (7 – 50)	34 (13 – 68)	0.34
Back pain now compared to preoperative pain*		3 (2 – 3)	4 (3 – 4)	<0.001
Leg pain now compared to preoperative pain*		2 (2 – 3)	2 (2 – 4)	0.37
Use of daily analgesics, mg				
	Opioids**	0 (0 – 40)	20 (0 – 60)	0.10
	Paracetamol	1000 (0 – 3000)	3000 (0 – 4000)	0.023
	NSAIDs	0 (0 – 0)	0 (0 – 400)	0.17
	Gabapentin	0 (0 – 0)	0 (0 – 600)	0.18
Work status, %				0.247
	Still on sick leave	42 (27 – 58)	59 (41 – 76)	
	Retired	26 (18 – 40)	22 (17 – 38)	
	Working	32 (20 – 46)	19 (10 – 31)	
Sports active, %		54 (39 – 69)	33 (20 – 47)	0.050
Walking distance, %				0.004
	< 100 m	5 (0 – 12)	24 (12 – 35)	
	100 – 1000 m	44 (15 – 66)	49 (18 – 70)	
	> 1000 m	51 (37 – 66)	28 (16 – 41)	
Satisfaction with surgical result, % (yes / no / unsure)				0.10
	Satisfied	62 (45 – 75)	61 (47 – 75)	
	Unsatisfied	10 (3 – 20)	22 (12 – 33)	
	Unsure	28 (20 – 50)	18 (8 – 29)	

Data are mean (SD), median (lower and upper quartiles) or frequencies (95% CI). * Back and leg pain compared to preoperative pain levels (0=no pain before, 1=gone, 2=much better, 3=somewhat better, 4=unchanged, 5=worse). **Morphine, oxycodone, tramadole, buprenorphine, fentanyl, or ketobemidone.

MAIN FINDINGS

Study I confirmed our hypothesis that preoperative IV dexamethasone 16 mg significantly reduced acute pain during mobilization. The clinical relevance is however debatable and we could not demonstrate an opioid sparing effect. **Study II** did not confirm our hypothesis that dexamethasone would prevent persistent postoperative pain. In contrast we discovered significantly higher pain levels in the dexamethasone group compared to placebo which may be of concern.

In **study III** our hypothesis that 500 mg of oral chlorzoxazone would reduce acute postoperative pain and opioid consumption in patients with moderate to severe pain after spine surgery, was not confirmed. We found no differences between groups.

In **study IV** the hypothesis that intraoperative ketamine would reduce postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency was confirmed. However, sedation was the only opioid related side effect reduced in the ketamine group. The hypothesis, that ketamine would reduce persistent postoperative pain 6 months postoperatively was confirmed by the finding of reduced back pain in the ketamine group.

DISCUSSION AND PERSPECTIVES

Study I and II

This trial confirmed our hypothesis that preoperative administration of IV dexamethasone 16 mg significantly reduced acute pain during mobilization from 2-24 h after primary lumbar disk surgery, when administered in a multimodal analgesicregime with paracetamol, ibuprofen and morphine. The effect was most pronounced from 8 to 24 h postoperatively, but smaller than stipulated in our initial sample size calculation (10 versus 12 mm on a 0-100 mm VAS-scale). The clinical relevance of this effect is discussable, but dexamethasone did bring the average pain scores from moderate to mild pain. Referring to the clinical target of 'no worse than mild pain' this reduction may have clinical relevance (54). The patient-titrated PCA-morphine consumption was similar in both groups and therefore, the significant reduction in pain during mobilization in the dexamethasone group may display the actual analgesic effect of 16 mg dexamethasone in this population. This reduction, less than anticipated, may reflect that dexamethasone was administered in conjunction with 3 other analgesics: Paracetamol, ibuprofen, and PCA-morphine. The overall mild to moderate pain scores may have influenced our assay sensitivity causing it difficult to obtain a larger effect size (55, 56). However, two trials succeeded in adding 125 mg methylprednisolone to a multimodal regime of paracetamol, celecoxib, and gabapentin and demonstrated pain relief after hip and knee arthroplasty, respectively (31, 32). It is still not clear what would be a sufficient dose of glucocorticoids to provide the greatest benefit outweighing harm (57).

Our 3 month follow up presented more patients in rude figures that had been treated for wound infection in the dexamethasone group, but this difference was not statistically significant. Our finding may be a signal of concern, but our follow-up 3 months after surgery was not powered to demonstrate small differences. One year postoperatively we discovered significantly higher pain levels in the dexamethasone group compared to placebo that may be of concern. These findings are in line with animal studies that have revealed mechanisms of glucocorticoid action indicating that they may have a role in the development of neuropathic pain postoperatively (58-61). However, these findings are controversial. Other studies have found that by inhibiting the release of prostaglandins, and production ofproinflammatory cytokines, excitatory amino acids, and growth factors in animal models, the development of neuropathic pain behavior can possibly be prevented (62, 63). The hypothesis that reducing acute postoperative pain reduces the risk of persistent postoperative pain was not demonstrated in study I and II (64). Two clinical trials exploring

the effect of glucocorticoids on persistent postoperative pain could not demonstrate this effect although those trials as well as our trial were limited in power because of the observed low incidence of persistent pain (65, 66). Therefore, at present, the long-term effects of glucocorticoids are conflicting.

Study III

This trial did not confirm our hypothesis and we found no analgesic effect of 500 mg of chlorzoxazone on pain after spine surgery for patients with moderate to severe pain. Further, opioid consumption, sedation, dizziness, vomiting and nausea were not significantly influenced.

Due to the sparse knowledge on the effect of chlorzoxazone it would have been ideal to measure the plasma concentration of chlorzoxazone in the patients to confirm the bioavailability. Previous analysis of plasma samples indicate a rapid absorption and rapid elimination of chlorzoxazone with average values of the elimination half-life of 1.12 +/- 0.48 hours (37). However, after general anaesthesia there is a risk of gastric retention potentially limiting the absorption of the orally administered tablets (67).

The trial includes a high potential risk of a type II error due to the very small difference in effect size between groups. One of the causes could have been the intraoperative administered analgesia and the fact that the patients could receive analgesics up to an hour prior to the starting point of the trial period. For analgesics like morphine with a longer duration of action than 1 hour this could have affected the outcome.

It could be argued that our patient population is heterogeneous due to the different spine surgery procedures, in terms of expected postoperative pain levels (11). But because the inclusion criterion was pain during mobilization > 50 mm, we consider the patient population homogeneous in terms of pain. The moderate to high pain levels contribute to assay sensitivity, and therefor this is not the most likely reason that we could not demonstrate any analgesic effect of chlorzoxazone (55).

Study IV

In this trial our hypothesis was confirmed. Intraoperative low-dose ketamine significantly reduced the postoperative 24-hour morphine consumption with approximately 35% after lumbar fusion surgery in chronic pain patients with opioid dependency. To the best of our knowledge, Loftus et al. has conducted the only current trial exploring the effect of intraoperative ketamine on the specific population of chronic pain patients with opioid dependency (43). Regarding opioid consumption they found a 30 % reduction at 24 hours, and a 37 % reduction at 48 hours postoperatively (43). These findings are similar to ours. However, there is a lack of standardization of perioperative characteristics and analgesics in the trial by Loftus et al. including the primary outcome. A source of strength in our trial is that the effect of low-dose perioperative ketamine was assessed on supplemental PCA morphine only. We found no difference in pain levels between groups. This is likely due to the equal opportunity of titrating PCA morphine to acceptable pain levels in the two groups (68). This promotes the reduced PCA-morphine consumption, as a true analgesic effect of perioperative low-dose ketamine.

Similar to previous trials on intraoperative ketamine for opioid naïve patients, and Loftus et al., we demonstrated a very limited effect on side effects (43, 45). Sedation was significantly, but not clinically relevantly, reduced in the ketamine group. In this specific patient population the low level of side effects could be a result of opioid habituation (69).

Six months postoperatively back pain and paracetamol consumption were significantly reduced, walking distance was increased, and patients had less disability on the Oswestry index score in the ketamine group compared with the placebo group. A weakness of our 6 months follow-up is the response rate of 65%. We do not know the condition of the non-responders. Due to the lack of correction for mass significance, there is a risk of type I error (false positive results). A review and meta-analysis investigating the role of ketamine in preventing persistent postoperative pain found that only one of nine pooled estimates of persistent pain demonstrated marginally significant pain reduction (51). Current evidence is still too meager to draw conclusions, but our study indicates that ketamine may have a unique role in preventing persistent pain in chronic pain patients with opioid dependency.

Methodological considerations

Basic analgesic regime and placebo

In study I and IV, dexamethasone and ketamine, respectively, are tested as adjuvants to a basic analgesic regime in the setting they would commonly be administered. In study I the basic regime consisted of paracetamol and NSAID. The combination of paracetamol and NSAID has been widely recommended and adopted internationally although the scientific evidence of the analgesic effect of these combinations is still meager (15). No systematic reviews or meta-analyses are available of the effect of combined paracetamol, NSAID, and steroid vs. paracetamol and NSAID alone, regarding established pain, or as prophylactic treatment. Due to the generally low to moderate pain scores induced by the surgical procedure in both groups this basic regime may have impaired the assay sensitivity and it was therefore difficult to demonstrate a clinically relevant additional analgesic effect of dexamethasone (55, 56).

In study IV, patients received paracetamol and continued with their usual opioid medication in the trial period. Continuation of usual opioids in the perioperative period is generally recommended in the literature to avoid insufficient opioid treatment and withdrawal symptoms (70). NSAIDs were excluded from the basic regime due to the conflicting data on NSAIDS regarding potential inhibition of bone healing possibly compromising the spinal fusion (non-union) (71, 72). Based on the relatively high opioid consumption and pain levels in both groups, the basic regime administered does not seem to have influenced assay sensitivity in this trial.

Basic analgesic regimes administered preoperatively and postoperatively hold a further challenge when used in pre-emptive analgesic studies or prevention of pain studies (study I and IV). A compounding difficulty in these analgesic studies is the circumstance where the analgesic intervention being tested is given

before it is known that the subject has sufficient pain to allow measurable decrease. Post hoc it can be evident that the basic analgesic regime was sufficient analgesia for some subgroups of patients in the study. In the matter of pain as primary outcome this will lead to compromised assay sensitivity due to low pain scores. In the case of analgesic consumption as primary outcome, low postoperative analgesic consumption might be interpreted as evidence of analgesic efficacy of the test intervention when in reality the subject had minimal pain to begin with.
Despite the use of a basic analgesic regime (study I and IV) and PCA morphine rescue analgesia (study I, III and IV) we consider our studies to be placebo controlled. We compared an active drug in one group with an inactive drug (placebo) in the other group, all other parameters remaining standardized. This allowed us to explore the effect of the active drug compared to placebo and at the same time acknowledging a possible placebo effect. At the same time the PCA morphine provided ethically correct rescue analgesia in the groups. The use of rescue medication will however interact with the VAS pain levels and can affect the "true" effect size of the intervention.

Considerations on multimodal analgesia
The original hypothesis regarding multimodal analgesia is that utilizing a combination of different analgesic modalities leads to better postoperative pain management and a subsequent reduction in opioid consumption and adverse effects.

In study I it is debatable whether dexamethasone is a clinically relevant adjuvant to paracetamol and NSAID due to the relatively small additional analgesic effect obtained, compared to the mild to moderate pain produced by the herniated lumbar disk procedure. Despite several previous studies demonstrating an, although modest, opioid sparing effect of dexamethasone, including a study similar to ours testing the addition of 16 mg dexamethasone to pregabalin on spine surgery (73), we could not reproduce this opioid sparing effect. When testing adjuvant analgesics in a multimodal regime the effect size will inevitably be reduced. A type II error cannot be rejected in study I. Further, study II indicates long-term complications from dexamethasone that might not outweigh the modest analgesic effect in the acute postoperative period. The neuropathic complications might be specific for procedures with a risk of nerve injury such as spine surgery. These findings confirm the need for testing the effect of multimodal regimes procedure-specifically and a huge need for exploring adverse effects of multimodal regimes as primary outcome.
In study IV our findings regarding the opioid sparing effect of ketamine are in line with a previous study on a similar patient population (43). Further we found a reduced incidence of sedation in the ketamine group. In relations to the ambitions of multimodal analgesia, it is noteworthy that we did not demonstrate other reductions in other opioid related side effects despite the large reduction in opioid consumption. This could be due to the study populations' compliance to opioids (69). It does however raise the question of the clinical benefits of opioid sparing in the acute postoperative period if side effects are not reduced? Knowledge on specific subgroups benefitting from opioid sparing and ketamine as part of a multimodal analgesic regime for spine surgery is still insufficient.

Outcome measures
In study I and III we chose pain (VAS mm) as the primary outcome using an established and validated nurse/investigator observer technique. In study I, we performed serial measures of pain carried out over 48 hours to explore the relatively long expected duration of action of dexamethasone. A series of measurements carried out at regular time intervals can build up a picture of the overall pain levels, but repeated measurements also holds the risk of multiple significance. The arithmetic sum of the scores over a set time can therefor provide an "area under the curve" against a time value, which utilizes the aggregate effect over a period of time. However, a limitation to this analysis is that patients with missing data are excluded from the analysis unless imputation of data is performed. Imputation is generally not recommended and because the extent of missing data in our trials was limited we chose to use complete case analyses. However when pain measurements are missing it might not be at random. Pain measurements can for example be missing due to high pain levels, sedation or nausea inhibiting mobilization, affecting the study results.

Study III is designed as a "treatment of pain" trial only including patients with VAS > 50 mm to assure assay sensitivity and to mimic the clinical use of the drug as a rescue analgesic for moderate to severe acute postoperative pain. To explore the maximum effect of chlorzoxazone in this situation we chose the primary outcome to be pain measured 2 hours after the intervention when the maximum effect of chlorzoxazone is expected. We also performed AUC to explore the aggregate analgesic effect of the drug over the entire expected duration of action.
In study IV we chose opioid consumption (PCA morphine) as the primary outcome because of the influence of ketamine on the opiate receptors. For trials using this analgesic consumption technique there is limited evidence regarding the robustness of the design (68). It has been hypothesized that studies that obtain equal pain scores between intervention groups should theoretically pose stronger evidence. This theory is based on the presumption that all patients independent of treatment groups will consume the amount analgesics they need related to their pain levels. This titration, reducing pain intensity to a level of acceptable pain, should lead to equal pain scores in both groups (68). In study IV the PCA morphine consumption was significantly larger in the ketamine group, with equal pain scores in both groups and we therefor consider our study design robust. However, the titration, (the PCA morphine consumption), might not only be determined by pain but can also be affected by the pharmacology of the drug. If patients make fewer demands of PCA for example because of nausea or sedation, then subjects who have received an ineffective test drug or a placebo may be unable to reduce their pain scores as far as they intent to. In study IV, sedation was significantly higher in the placebo group but to such limited degree that the clinical relevance is discussable. This in conjunction with the equal pain scores in both groups confirms our validity.

There is however a need for more examination of analgesic consumption as an outcome measurement.

Multiple significance
In study I, III and IV we used Bonferroni's correction for multiple comparisons. We chose this approach to help ensure no type 1 errors were made in the secondary outcomes. But using this rather conservative method also means a greater risk of ignoring a relationship that is real and performing a type 2 error.

Study II and the 6-months follow-up in study IV consists of a long-term follow up based on explorative secondary outcomes that the original trials were not powered to detect. Many of the questions in the questionnaires regard the same topic and we would therefore have to do multiple corrections. As we consider these outcomes hypothesis generating, we chose not to correct for multiple comparisons and of course interpret the results in respects to the increased risk of type 1 errors.

CONCLUSIONS

This thesis explored adjuvant analgesics for spine surgery. We found a significant although moderate analgesic effect of dexamethasone and discovered some potentially concerning negative long-term effects of this drug. We demonstrated that chlorzoxazone does not seem to have any immediate analgesic effects as an adjuvant for pain after spine surgery. And lastly we found that intraoperative ketamine reduced postoperative opioid consumption and persistent pain 6 months postoperatively in chronic pain patients with opioid dependency.

FUTURE DIRECTIONS

- Regarding future multimodal analgesia trials it is important to not just add more adjuvant analgesics to several other analgesics which will most likely just lead to reduced assay sensitivity. New research must use trial designs and populations that enable the assessment of both mono- and poly-interventions, and potential interactions among the combinations. Trials powered to explore adverse events are much needed.

- Future dexamethasone studies should investigate the optimal dose in procedure specific trials. The exact dose of glucocorticoids at which potential harm outweighs benefit is unknown. Also, large studies powered for evaluation of safety aspects such as wound infection are warranted. Our study is hypothesis generating for future properly sized studies investigating long-term effects of perioperative glucocorticoids on human postoperative pain.

- Chlorzoxazone studies elaborating on our findings are warranted. Further, the study highlights the need of future randomized trials of chlorzoxazone in chronic low back pain patients, as this treatment is currently not supported in the literature.

- Regarding ketamine as an analgesic for postoperative pain following questions remains unanswered: The optimal dose and regimen of administration of ketamine and regarding this at what point do higher sub-anaesthetic doses increase side effects? Should ketamine be aimed at specific subgroups such as opioid dependent patients or chronic pain patients and in this case what are the cut-off levels? Does ketamine prevent persistent postoperative pain?

ABBREVIATIONS

ASA	American Society of Anaesthesiologists
AUC	Area under the curve
BMI	Body Mass Index
CI	Confidence interval
EQ-5D	EuroQol 5D questionnaire
IV	Intravenous
NMDA	N-methyl-D-aspartate
NSAID	Non-steroidal anti-inflammatory drug
PACU	Post anaesthesia care unit
PCA	Patient controlled analgesia
PCM	Paracetamol (acetaminophen)
PONV	Postoperative nausea and vomiting
SD	Standard deviation
SF-36	Short Form 36 survey
VAS	Visual analogue scale
wAUC	Weighted area under the curve

SUMMARY

Increasing evidence indicate that pain is insufficiently treated following surgical procedures. It is essential that pain treatment is effective with a minimum of side effects in order to promote postoperative rehabilitation. Multimodal analgesia is most likely an important strategy in reducing postoperative pain. Combinations of different analgesics with different mechanisms of action may have an additive analgesic effect with fewer side effects compared to using a single drug. However, there is still a pronounced lack of documentation for the effect and side effects of these multimodal analgesic regimes. More than 6,000 spine surgeries are performed annually in Denmark and spine surgery has been associated with high levels of pain compared to other surgical procedures. Therefor we considered spine surgery to pose a group of well-defined surgical procedures and we used this model to investigate the efficacy of 3 adjuvant analgesics aiming to improve the multimodal approach in pain management.

In **study I and II** we hypothesized that preoperative IV dexamethasone 16 mg would reduce acute postoperative pain, opioid consumption and persistent pain after lumbar disk surgery. We found that dexamethasone significantly reduced acute pain dur-

ing mobilization. The clinical relevance is however debatable and we could not demonstrate an opioid sparing effect. Further we discovered significantly higher pain levels in the dexamethasone group compared to placebo 1 year postoperatively.

In **study III** we explored the effect of 500 mg of oral chlorzoxazone on acute postoperative pain and opioid consumption in patients with moderate to severe pain after spine surgery and found no effect of chlorzoxazone compared to placebo.

In **study IV** we hypothesized that intraoperative ketamine would reduce postoperative opioid consumption and persistent pain after spinal fusion surgery in chronic pain patients with opioid dependency. We found a significantly reduced opioid consumption in the ketamine group and a reduced level of persistent pain 6 months postoperatively.

In conclusion, dexamethasone and ketamine are potential adjuvant analgesics for postoperative pain. Possibly ketamine also inhibits the development of persistent pain. Chlorzoxazone has no immediate effect as an adjuvant in acute pain management.

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