Measurement of drug concentration and bacterial contamination after diluting morphine for intrathecal administration: An experimental study. (MoCCa trial)

Aart Jan W. Teunissen, MD[1], Mark V. Koning, MD[2], Bart J. de Bruijn[1], Elisabeth J . Ruijgrok, PhD[3]
1 Maasstadziekenhuis, Anesthesiologie, Rotterdam, The Netherlands
2 Haaglanden Medisch Centrum, Anesthesiologie, The Hague, The Netherlands
3 Erasmus Medical Center, Pharmacy, University of Rotterdam, The Netherlands

Introduction:
Intrathecal administration of morphine is an effective method of analgesia and the duration of analgesia and the incidence of side-effects are dose-dependent. The therapeutic range is between 100 and 300 mcg, which requires precise concentrations to administer the correct dose. Over 500 mcg there is a risk for late respiratory depression and the incidence of pruritus and nausea are increased.[gehling, bailey]. Therefore, delivering a morphine dose within the therapeutic range is paramount for safety. Since concentrations of 1 mg/ml or 10 mg/ml of morphine are commonly used, this has to be diluted to useful concentrations. Manual dilution may come with concentration errors and microbial contamination.

Aim: This study aims to measure the accuracy of morphine concentration and contamination of manual dilution of morphine in 3 different ways.

Methods:

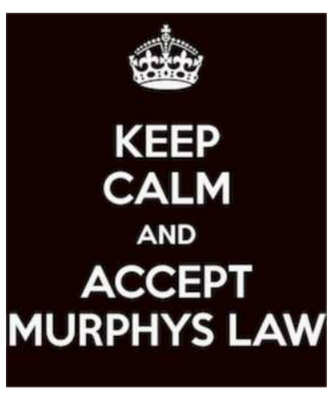
- 25 experienced anesthesia providers were asked to prepare a mixture of bupivacaine and morphine, according to predefined methods (table 1).
- The target concentrations were 2.0 mg/ml bupivacaine and 60 mcg/ml morphine.
- Ready-to-use ampoules, provided by the pharmacy department, were used as a control group. These ampoules differed in concentration of bupivacaine, which was 2.5 mg/ml.
- The subjects received written and oral instructions for preparation of the syringes.
- It was stressed that the mixtures needed to be as clean and precise as possible. Blue nitrile gloves and caps were worn by the subjects. No time constraints were added.

Results:

- Figure 1 and Table 2
- In group 1 there were 3 outliners that could potentially result in respiratory depression, this method should not be used
- There was no relation detected between the anesthesia provider and the accuracy of the morphine concentrations (P=0.462).
- Four samples, equally spread over all four groups, had positive cultures with spore-forming aerobic gram positive rods (p=1.000).
- A fiber was detected in one sample (group 2).

Conclusion:

- Diluting a medicine manually is prone for elevated concentrations.
- Contamination occurred in all groups and is a serious risk
- We recommend using prepared solutions by the pharmacy department.
- If these are not available, it is advised to use the lowest possible starting concentration, using as little dilution steps as possible and use protocols that have an mixing step in the creating of a solution or shaking syringes after dilution.
- In clinical studies, the drug should be produced by the pharmacy, since manual dilution can cause an erroneous dose.



MAASSTAD ZIEKENHUIS
een santeon ziekenhuis

H+ MC

Erasmus MC
Universitair Medisch Centrum Rotterdam

Table 1

Group	Preparation steps					
1	Aspirate 1 ml of 10 mg/ml morphine	Inject in a 100 ml NaCl 0.9%-container	Aspirate 3 ml of this mixture in a 5 ml-syringe	Add 2 ml of 5 mg/ml bupivacaine		
2	Aspirate 1 ml of 10 mg/ml morphine in a 10 ml-syringe	Dilute with 9 ml NaCl 0.9% in the same syringe	Dispose 9 ml of this mixture to achieve 1 ml of 1 mg/ml	Dilute with 9 ml NaCl 0.9% in the same syringe	Aspirate 3 ml of this mixture in a 5 ml syringe	Add 2 ml of 5 mg/ml bupivacaine
3	Aspirate 1 ml of 1 mg/ml morphine in a 10 ml-syringe	Dilute with 9 ml NaCl 0.9% in the same syringe	Aspirate 3 ml of this mixture in a 5 ml syringe	Add 2 ml of 5 mg/ml bupivacaine		
Pharmacy	Aspirate 5 ml of a ready-to-use ampoule					

Figure 1

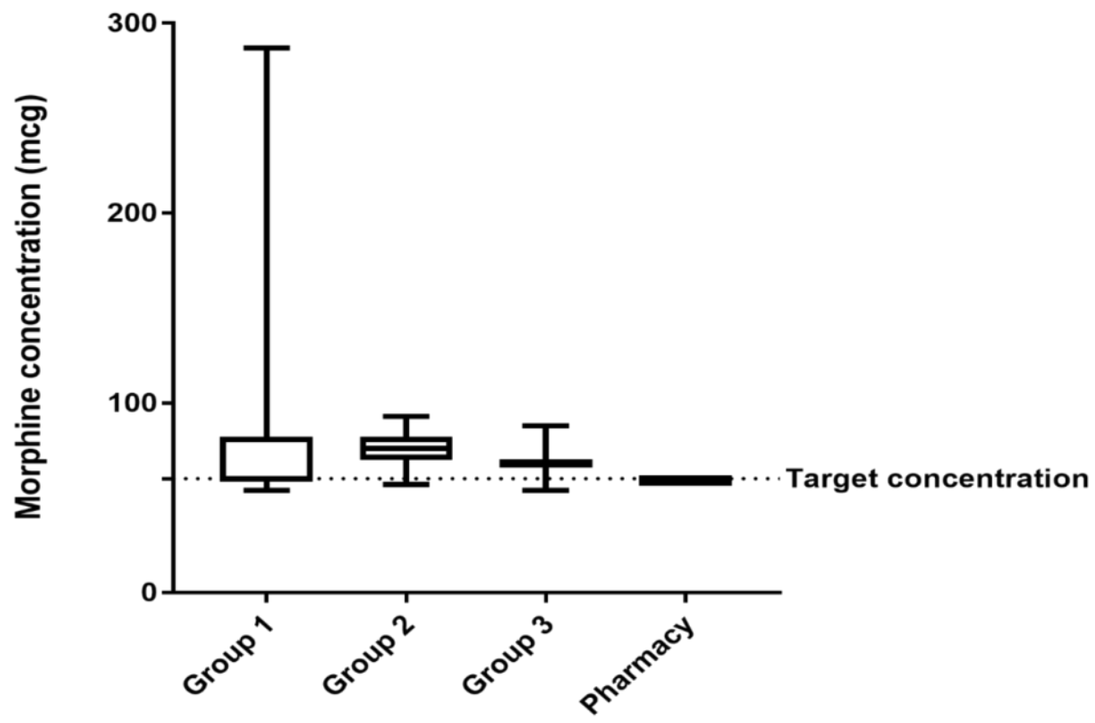


Table 2

		I	2	3	Pharmacy
Morphine	Microgram	60 (59-80)	76 (70-82)	69 (66-69)	59 (59-59)
	95% Confidence Interval	59-110	72-80	66-71	59-59
	Out-of-range (<80%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Out-of-range (>120%)	7 (28%)	18 (72%)	3 (12%)	0 (0%)
Bupivacaine	Milligram	1.98(1.93-2.01)	2.00(1.94-2.04)	1.97(1.92-2.01)	2.54(2.54-2.54)
	95% Confidence Interval	1.73-2.06	1.95-2.03	1.91-2.00	2.54-2.55
Contamination	Number	1	1	1	1